

OCT 21 1952

30

THE CHICAGO MEDICAL SCHOOL
QUARTERLY



VOLUME 14, NUMBER 1

OCTOBER 1952



CONTENTS

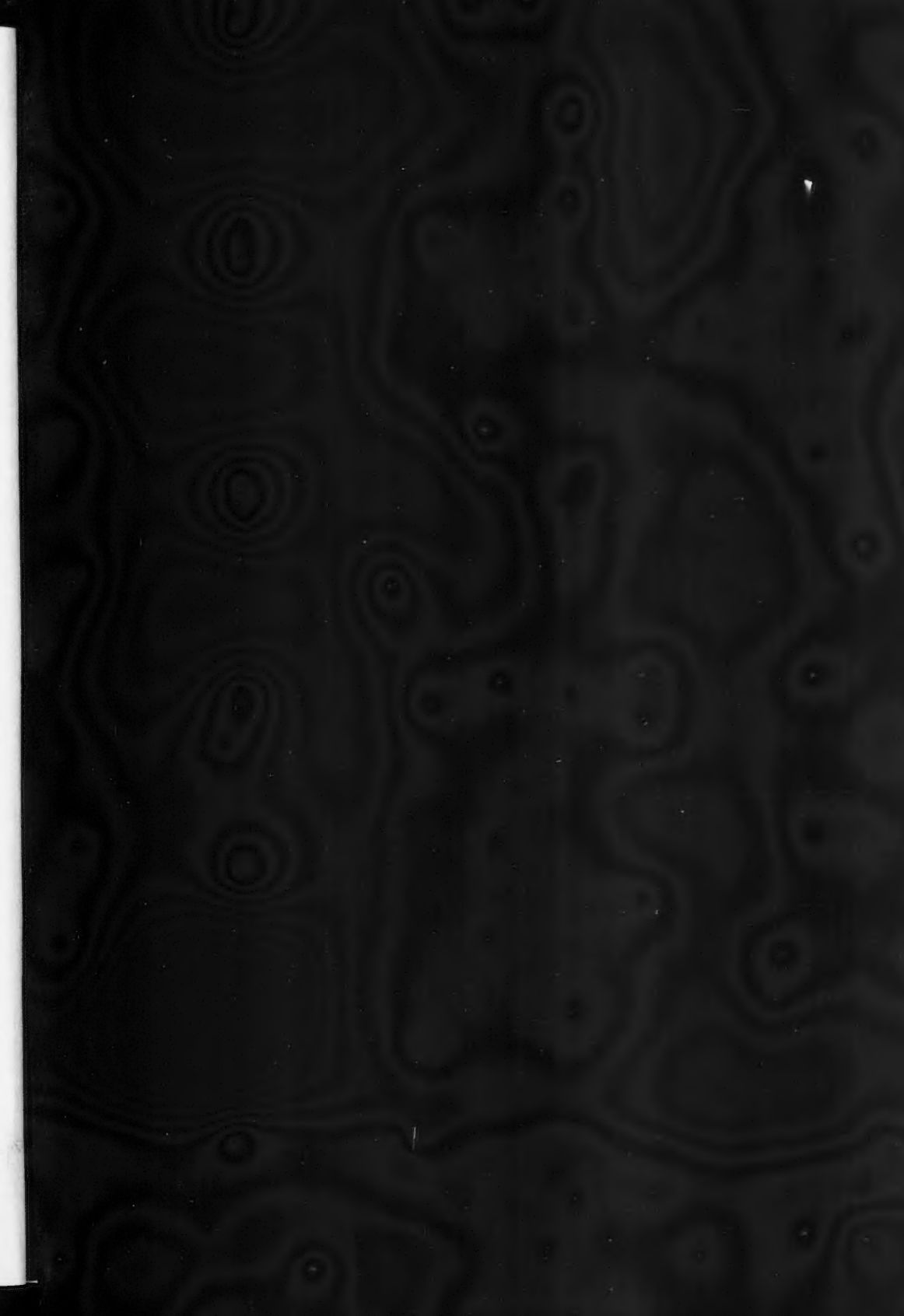
ORIGINAL ARTICLES

Symposium:

The Cardiac Neuroses	1
Aldo A. Luisada, M.D.	
A Psychosomatic View of Cardiovascular Disease.....	8
H. H. Garner, M. D.	
Infectious Mononucleosis	13
Israel Davidsohn, M.D.	
Some Recent Concepts in Carcinogenesis.....	21
A. C. Ritchie, M.D., and Philippe Shubik, M. D.	
Acute Pancreatitis	25
Martin M. Kirshen, M.D., F.A.C.P.	
Clinicopathologic Conference	29

FEATURES

Book Reviews	40
Abstracts	41
School Notes and News	43
Faculty News	44
Alumni News	46
Student News	47
Organization News	47



3474

THE CHICAGO MEDICAL SCHOOL QUARTERLY

VOLUME 14

OCTOBER 1952

NUMBER 1

SYMPOSIUM:

A discussion of some common cardiovascular diseases by a Psychiatrist-Neurologist, H. H. Garner, M.D., and a Cardiologist, Aldo A. Luisada, M.D.

THE CARDIAC NEUROSES*

ALDO A. LUISADA, M.D.**

Some of you asked me to lecture on *functional disorders of the heart and circulation*. Apart from disturbances of cardiac rate and rhythm, these include cardiac neuroses, anxiety syndromes, and neurocirculatory asthenia. Before describing them, it is necessary to examine various problems concerning the multiple relationship between the central nervous system and the various organs of the body.

Psychosomatic Medicine and the Various Trends of Medical Thought

A term which is increasing in popularity is that of "psychosomatic medicine". I am obliged to say that it is a bad expression, which is sometimes made worse because of its untoward use by unqualified people. The meanings given to this term have been increasing up to the point that it might call for a new specialty involving the fields of medicine, surgery, pathology, and psychiatry!

From the Stone Age to the 16th Century, "Psychosomatic Medicine" was "Medicine". This was so because bacteria and viruses were unknown and "evil spirits" or "unknown forces" were

thought to enter the body. These had to be exorcised, or chased out of the body, by means of incantations or various other psychological methods. The doctors tried suggestion, psychology, make-believe, or witchcraft—all of which act on the psyche of the patient. In many cases, they obtained wonderful results. But the failures were numerous. In the rare cases where the results obtained were considered "impossible", people spoke of "miracles". Even at present many patients still seek to obtain a miracle.

In spite of this generalization, there have been periods in the history of medicine where a systematic study of the patient was made, physical examination was practiced, attempts at systematic therapy were made, and several drugs were used. Among the great schools of the ancient times, one of the best known is that of Hippocrates, even though Hippocrates followed a long series of older physicians. The school of Galen, who dissected animals and studied the movements of the heart *in vivo*, and that of Herophilus, who dissected criminals, represent two forward steps in the History of Medicine. The studies of the Arabic physicians of the late Middle Ages were also noteworthy.

In spite of the many advances, many of the drugs were given empirically or

* Lecture to Senior Students of The Chicago Medical School.

** Associate Professor of Medicine and Program Director of Cardiology of The Chicago Medical School, under a Teaching Grant of the National Heart Institute, U.S.P.H.S.

on the basis of erroneous beliefs. Moreover, we can ascribe some of the results obtained, not to the action of drugs, but to suggestive effects. Do not forget that, whenever a physician prescribes a medicine and sincerely believes in its effect, an important suggestive therapy is used in addition to drug therapy. Many old doctors believed in what they were doing and obtained good results which could not be explained by simple pharmacology.

This trend of medicine continued to the era of Napoleon. With Morgagni, Corvisart, Laennec, and other physicians, attention was focused on the organic, structural changes of the various organs. Dissection and comparison of pathological specimens with the histories of the patients were very helpful and led to descriptions of *anatomic-clinical syndromes*. This represented a complete swing of the pendulum to the *organic era of medicine*. Functional disturbances were ascribed to definite organic lesions and correlation was attempted between diseases, functional disturbances, and pathological specimens. Although the principle was carried too far, we must say that this trend was extremely fruitful. Even at present, our knowledge is not sufficient to exclude the possibility that organic changes, consisting of fine histochemical modifications (or even finer molecular changes) may be the cause of psychoses or other mental disturbances. A lot has been said about organic disease following mental strain or injury, but very little has been said about mental troubles following minute structural changes in the central nervous system — because we know very little about these.

Twenty years ago, an opposite movement was started. Correlation between certain clinical histories, certain phenomena, and certain unexpected or negative pathological findings, gave rise to the concept of "psychosomatic medicine". This term means: (1) that some disorders of the body are due to disturbances of the mind, and (2) that these disorders might be treated by acting on the mind and not on the body. Now, even if the first part were true, this does not mean that the second is also necessarily true; it may be impossible to reverse a trend,

and it may be necessary to act through physiological-organic means once the organic changes have started.

There is one thing which I want to emphasize now. This trend, which may be sound if kept within the proper limits, has been misrepresented by irresponsible or poorly trained physicians and has led to tremendous exaggerations. At certain medical meetings, one can hear physicians talk uncritically about "one case" — that was not properly analyzed, was poorly studied, and was not followed by postmortem examination. From these single, uncritically examined cases, the same physicians extend conclusions to hundreds or thousands of other patients, until one has the impression that we are going backwards toward the Middle Ages and we are going to again have "Witch Doctors." This is why, even though there may be some good in this new trend, one should consider with criticism the facts presented and the conclusions drawn from them.

Organic and Functional Disorders

How should we consider the relationship between body and spirit, between organic and functional disorders? This is a question which is definitely not easily solved because, while we know something about the body, we know much less about the mind. One should not lose the point of view of an anatomist and a physiologist. We have organs; their functions are controlled by nerve stimuli, namely by the nervous system. The skeletal muscles are ruled by a section of the nervous system; most of the other organs are controlled by another section, the autonomic nervous system. The lower nerve centers are controlled by higher centers, not always by the cortex. Actually, the basal ganglia represent rudimentary centers which act independently of the will. While it is impossible to voluntarily modify the rate of the heart or the secretion of a certain gland, this effect may be obtained indirectly through the cortical representation of mental pictures, emotion, and excitement, leading to an increase of function of these cortical areas and hence to changes in the function of end organs.

The endocrine system correlates certain functions, increases or decreases the

rate of others, and is again indirectly controlled by the nervous system. On the other hand, it may also influence the processes of the latter.

Most organic diseases (including those caused by microscopic agents) result in gross or microscopic structural changes and also *give rise to functional disturbances*. In the case of the heart, organic processes (myocarditis) are revealed by tachycardia, extrasystoles, flutter or fibrillation). The functional disorder may be based on histological or biochemical changes which sometimes are not easily recognized. One of the reasons for difficulty in recognition is that it is difficult to study the chemical processes of thousands of cubic millimeters of myocardium. This might be done in a few selected cases or, with newer methods, by researchers of the future.

Functional disturbances may be the cause of structural changes. One example is represented by paroxysmal tachycardia. We know that such paroxysms of rapid heart action may follow psychic excitement, probably through increased stimulation of sympathetic fibers and increased adrenaline secretion. The relationships between the brain and the pituitary gland, and between the pituitary and the adrenals, bring several possibilities to mind. Prolonged or extreme tachycardia may be followed by myocardial damage, which is revealed by the so-called post-tachycardial syndrome. It is less known that a ventricular flutter may be precipitated by excitement and that even ventricular fibrillation or ventricular standstill may occur, especially if the heart were previously damaged. Thus, *sudden death* due to cardiac arrest or ventricular fibrillation may be provoked by acute excitement and there are proven cases where this happened even in normal individuals. It is probable that the excitement was followed by nervous stimuli causing constriction of the coronary vessels, and by the secretion of hormones which, at the same time, caused an overwork of the heart. If the same mechanism were in action for longer periods of time but with less intensity, ischemia of the myocardium might result and this might eventually lead to structural changes.

Another possible example is that of *arterial hypertension*. You have probably heard a lot about this in your course on psychosomatic medicine. You have probably heard that, in most cases, hypertension is a purely functional syndrome connected with emotion and excitement. There is certainly some validity to this, but we do not know whether this is true or whether mental stimuli represent only a predisposing element. We know that excitement, through secretion of ACTH, stimulation of the vasoconstrictor nerves, and ischemia of the kidney, may lead to paroxysmal hypertension, but we do not know whether this may later lead to continuous hypertension. Whenever the heart is more or less extensively damaged (as in coronary heart disease, fibrosis of the myocardium, or myocarditis), it becomes extremely sensitive to any nervous impulse and, therefore, indirectly, to excitement.

We know that, in cases with minor cardiac lesions, excitement and emotion may be followed by *acute dilatation of the heart*. In some of these cases, the onset of *congestive failure* is provoked by excitement, and this is why, in patients with rheumatic or coronary heart disease, we try to avoid not only physical exertion, but also excitement.

Another example is *paroxysmal pulmonary edema*. Sudden excitement may lead to widespread vasoconstriction, with increased resistance in the systemic circulation, squeezing of the small arterial and venous vessels, and displacement of a large mass of blood toward the right heart and the lungs. This causes increased pressure in the pulmonary capillaries and edema. Increased peripheral resistance and increased inflow may also lead to left ventricular failure and acute pulmonary edema if minor damage to the heart is present.

Another possibility to consider is that of a violent *carotid sinus reflex*. This reflex is part of a normal physiological adaptive mechanism but, in patients with a hypersensitive carotid sinus or in the presence of excitement, there may be a violent reflex causing a cardiac disorder.

There is no reason for me to go too deeply into the problem of *peripheral vascular diseases* because you all know

that excitement may lead to the *Raynaud phenomenon*, namely to gradual spasms of the vessels of fingers, with pallor or cyanosis — which is not uncommon in young people.

Organic Disease plus Neurosis

Another point which we should take into consideration is that *an organic disease may be either the cause of a neurosis or may be associated with a neurosis*. The difficult part of the doctor's task is that of finding out how much is due to the basic organic disease and how much to the neurosis. In the cardiovascular field, the most common neuroses are usually precipitated by a certain diagnosis, or a certain word, which in the mind of the patient is associated with a fearful picture. These words vary from time to time, from country to country, and from place to place, according to the average knowledge gained through reading, talking, or whispering. For example, when I was a student, the most fearful words were "angina pectoris" or "heart disease." Ten years later the word "hypertension" was frequently a cause of disorders. A few years later, I found out that "hypotension" occasionally was the cause of a neurosis. The emphasis has now changed. We don't talk so much about angina pectoris because we believe that patients who die from coronary heart disease die of myocardial infarction, so that now the terms "coronary thrombosis" or "myocardial infarction" have become fearful. "Coronary heart disease" and "rheumatic heart" are also frequently feared. Another term which has been feared for over 50 years is "murmur." Cardiac murmur, in the minds of many, is a term implying impending death; therefore, the patient is afraid, and being afraid, becomes more and more sick. One example is very vivid in my mind because I saw the patient yesterday. This was a 30-year-old woman with rheumatic heart disease and a minor degree of mitral stenosis which had caused no discomfort until now. The patient has two children and has had a normal family life. One day, a doctor told her that she had a "murmur" and another doctor said that she had a "rheumatic heart." She then began to lose sleep and developed a neurosis, so that she became a nervous wreck.

Page Four

I once saw two students examining a cardiac patient in a ward. The patient was doing fine, but when she heard the students discussing whether the murmur was systolic or diastolic, grade 4 or grade 6, "beautiful" or not, she had a fit of convulsions, which precipitated congestive failure. We had to work on that patient for months before she could return to her previous stage of mental and physical balance. This should teach you to be careful when speaking in front of patients. On the other hand, do not forget that patients are liable to misinterpret too much caution or complete silence from the doctor. There are cases where a doctor is unable to make a diagnosis. If he fails to explain the reason for his silence, the patient starts worrying: "there must be something mysterious, so that nobody wants to explain it; this means something dangerous!" Therefore, you should always try to give a logical explanation. In most cases, you can tell the truth in a nice, kind way. You remember the patient I saw yesterday? She asked me abruptly, "Do I have a rheumatic heart or not?" Knowing the meaning she attributed to the word "rheumatic," I was tempted to lie, to say, "No, you don't." But, instead of that, I tried to explain by means of a parable, so that she was reassured. She asked, "What kind of prescriptions are you going to give me?" I said, "You should go dancing at least twice a month." With that, she was happy. She had no functional disorders of the heart and did not need to restrict her activity. I hope that her neurosis will gradually decrease and subside.

How do we evaluate these functional cardiac disorders? In some cases, when you see the patient crying or saying foolish things, it is easy to understand that excitement may be the cause of the clinical disorder. In others, the diagnostic problem is more difficult. The patient may be cold and objective and may describe very carefully this or that symptom. Only small details may give the clue to a correct diagnosis.

Cardiac Neuroses and the Anxiety Syndromes

Which are most frequent symptoms? One is *precordial pain*, usually unasso-

The Quarterly

ciated with exertion, frequently beyond the left anterior axillary line (or localized to a small area of the precordium), and penetrating, knife-like, or continuous in character. Another symptom is a *sensation of pressure*, which is not described in the same way as the deep oppression of the coronary heart patient. Another one is *palpitation*. Palpitation is the consciousness of the motions of one's own heart. Some of these patients become heart conscious because they have premature beats or because they experience an increase in blood pressure when excited. Another sensation is *shortness of breath*. If you ask your patients what they mean by that expression, they will explain that their shortness of breath is due to a *sighing respiration*. Sometimes they have deep repeated sighs, hyperventilate, then become dizzy and stop breathing for a while because there is not enough carbon dioxide in the blood to stimulate the respiratory center. A clinical picture like this is suggestive of some kind of *anxiety neurosis*.

When Charcot developed his concept of hysteria at the Salpêtrière, any clinical picture which could be cured by suggestion was considered *functional* and due to a neurosis; the other clinical pictures were considered as caused by organic lesions. This concept is not admitted any more, because we know that we can sometimes cure organic diseases (or their after-effects) by means of suggestions, while in other cases, a long lasting neurosis may defy any treatment. Moreover, a patient frequently has both an organic disease and a neurosis and the two may be either connected or entirely unrelated. I want to report an example which I shall never forget.

An old farmer came to the Hospital complaining of "ants crawling through his abdomen up to his mouth." We examined the patient from every point of view and found absolutely nothing. The patient was proctoscoped and again nothing was found. But, questioned the following morning, the patient said, "I'm cured. I feel fine; no more ants." The patient was supposed to be presented to students as a case of "neurosis." Three weeks passed and we found that the patient was rapidly losing weight. Three

months later the patient was dead. Autopsy disclosed a nonobstructing cancer of the descending colon. The organic disease had been the cause of a curious mental picture which was completely relieved by a procedure which was effective only because it was applied at the spot where his attention was concentrated. In this case, according to Charcot, one should have diagnosed pure hysteria while, in reality, this was a mere superstructure.

I could multiply these examples and find many more in the field of heart disease. I have seen patients who had an organic stenosis of the mitral valve and lived happily for many years. Then suddenly, because of overexertion or emotion, they became conscious of their hearts — probably because of extrasystoles. Their doctor made the correct diagnosis, but, from that moment on, the patients became nervous wrecks and were unable to work or have a normal family life.

Organic lesions and mental disorders are frequently associated. Some patients have severe structural lesions and no functional disorders. Others have severe functional disorders and no lesions. The most common occurrence, however, is the co-existence of both. They may be either related or unrelated. Patients with coronary heart disease may recover after a myocardial infarction, refuse to pay attention to the doctor's advice, go back to work, and be active for many years. Sometimes they die in the process, but they were active and happy until the last day. Other patients suffer from a small infarction with a mild clinical picture and yet they become "cardiac cripples," afraid of everything, and unable to live normal lives.

Some people are unable to face facts. As long as they have 100 per cent health, they work, but the moment they have only 95 per cent health, they talk about shooting themselves. They usually don't shoot themselves, but do become social liabilities. This is a very important problem for the cardiologist — to rehabilitate cardiac patients who have been crippled by their own imaginations.

Neurocirculatory asthenia presents a curious clinical picture. It is common

in males during wars or emergencies while, in peacetime, it is present mostly in females. This syndrome, described by Da Costa, cannot be defined exactly because of great variations. The patients mostly complain of pain, exhaustion, dyspnea, palpitation, precordial pain, fainting attacks, and tingling sensations. In time of war, the most common complaint is exhaustion. I have seen letters written from the battlefield saying, "I feel tired, tired, tired . . . When I get up in the morning I am more tired than when I go to bed . . ."

Dyspnea is usually not connected with exertion. Palpitation may be related to emotion but, again, it may be entirely unrelated to it. Precordial pain is the least typical part of the picture, being sticking, circumscribed, and not radiating. It is sometimes connected with flatulence. Tingling sensations sometimes spread to the entire left arm and are not limited to the area innervated by the ulnar nerve, as in angina pectoris. The picture may be different if the patient reads medical books or was associated with someone who had coronary heart disease, so that one cannot always believe the patient's statements. There are cases where a husband and wife both have angina pectoris and both die of coronary heart disease. Therefore, the simple fact that there are two patients in the family does not mean that one has an imaginary disease. Brothers and sisters frequently have coronary heart disease or hypertension because hereditary factors predispose them to these diseases.

The physical findings in neurocirculatory asthenia are limited. The patient may have tachycardia, an inverted T wave in the chest leads of the left side, and a slight increase in blood pressure.

Could the feeling of exhaustion be related with a *stress syndrome*? I am convinced that this "stress syndrome" is still incompletely understood. We know that severe stress is followed by the secretion of anterior pituitary hormones and of other hormones. If this stress is repeated, exhaustion of these glands may take place, so that the next stress or even the usual normal stimuli of life cannot lead to the normal secretion of hormones. We can therefore understand

that a person may feel tired if these glands are functionally exhausted. The extreme exhaustion may favor the establishment of shock. According to another theory, neurocirculatory asthenia might be due to a hypothalamic disorder. Proof of this, too, is lacking.

Organic and Functional Effects

Following Mental Stimulation

The first example of this is an old one. There was a movement towards "psychosomatic" medicine in Germany in the decade following World War I. Several centers attracted numerous patients who were treated by self-appointed doctors (shall we call them witch doctors?) for ailments of the most varied nature, including warts and other skin disorders. Some of these came back cured. This is an example of a *structural change cured through suggestion*.

There are many sanctuaries in the world where believers go, exerting suggestion upon themselves and upon each other. The patients congregate, talk together, hope together, and pray together before being submitted to the healing function—whatever that is. Patients with tubercular spondylitis and rheumatoid arthritis went to some of these centers as cripples and came back "cured." It is likely that the structural lesions were modified several months following the impact of the initial suggestion but the subjective improvement was sudden.

The results obtained by Kempner with the *rice diet* in hypertensive patients cannot be duplicated elsewhere because his patients are isolated from the rest of the world and stay in line for hours before being examined in order to receive their diets. During this time they talk together, exerting reciprocal suggestion. As a result, their blood pressure gets lower, but, as soon as they get back to civilization, their high blood pressure returns. The same thing is true for many of the spas where people are treated for cardiovascular disorders. They drink certain waters, take certain baths, or cover themselves with mud. Even if the baths are not too useful, there is a phenomenon of collective suggestion which is certainly helpful.

In order to show you how we can explain some of these cases, I am going to

report an example which happened last year here in Chicago. There was a 30-year-old woman suffering from rheumatoid arthritis. She had been bedridden for 5 years. Her doctor was thinking about giving her ACTH, but was undecided. Suddenly, the mother of this patient had a cerebral attack. When the patient heard about it, she got up from bed, walked to a cab, went to her mother's home, and started nursing her. The mother lived 12 days during which the patient nursed her. When the mother died, the patient collapsed, was brought back to bed, and has been bedridden ever since.

"Power of suggestion," you may say. However, we know that cortical impulses reach the lower centers and that these may cause stimulation of the pituitary gland. Increased secretion of ACTH may explain a temporary improvement, similar to that obtained therapeutically in other cases of rheumatoid arthritis. This shows how the mind can dominate the body through a well understandable physiological process.

The Doctor-Patient Relationship

Now I wish to give you some advice. Be careful of what you say in the presence of a patient. Don't tell too much, but don't be too secretive. Try to give a logical explanation for the disturbances and for your treatment.

Don't be too abrupt. When you examine a patient, remember that you are dealing with a human being, and try to have sympathy for your patient. You cannot treat the patient well if you don't sympathize with his problems. When you formulate your treatment, try to be conscious of your patient as an individual, and consider all the possible inconveniences which may arise from undue administration of drugs, undue suggestion, or from lack of suggestion. Remember that psychotherapy is not necessarily dealt with words—it may be part of the results obtained with drugs, with an x-ray, or with an electrocardiogram. I may as well tell you that, if you have in mind to see 70 patients a day in your practice, you will be bad doctors. Even a healer, a miracle maker, cannot make 70 miracles a day!

Conclusions

The *functional disorders of the heart* include various entities called cardiac neurosis, anxiety syndrome, and neurocirculatory asthenia. They are poorly limited clinical pictures, at the borderline between psychiatry and cardiology, and their causes are still incompletely understood. On the other hand, differential diagnosis between these syndromes and purely cardiological pictures is often necessary and usually not difficult. It is likely that minor structural lesions or mild functional disorders of the heart and vessels cause, in predisposed individuals, all symptoms reported by these patients. On the other hand, neurocirculatory asthenia may be related to the stress syndrome through an easily understandable mechanism.

Psychosomatic medicine is a poor name for an old concept—that of the indivisible unity of mind and body. While it is undeniable that many "organic" diseases are favored and even caused by mental processes and may occasionally be cured through suggestion, the opposite is also true and is too often forgotten: hormonal or biochemical disorders and structural changes may be the cause of mental disorders.

Mental causes of many cardiovascular diseases, from rheumatic fever to hypertension, from angina pectoris to neurocirculatory asthenia, have been advocated without scientific proof. While a serious investigation into all factors contributing to or favoring disease (including the psychic elements) is useful, unwarranted statements or distortion of facts might cause a regression of Medicine to backward stages.

Cardiovascular neuroses are not always isolated pictures. Sometimes they are an integral part of the picture because they are strictly connected with the main cardiac disorder. Other times, they are an unrelated superstructure which may be treated separately.

Suggestion is an integral part of the Art of Medicine. It is not necessarily developed by mental specialists and is frequently used most effectively by general practitioners or internists. Many successful results by means of drugs,

(Continued on page 39)

A PSYCHOSOMATIC VIEW OF CARDIOVASCULAR DISEASE

H. H. GARNER, M.D.*

No other body system is used as frequently as the cardiovascular system, in a symbolic sense, to refer to love and to hate. We are familiar with such expressions as: "loving with all of my heart," "a warm heart," "heart-throbs," "heart-felt." Words indicating lack of love or the presence of hate, such as "hard-hearted," "cold-blooded," and "heartless," are familiar daily expressions.

Disturbances referable to the heart are among the most common symptoms of psychogenic origin. Tachycardia, irregularities, and dyspnea associated with tachycardia are so frequently mentioned as subjective manifestations of anxiety that this relationship is now common lay knowledge. The heart has been described as the specific sense organ of anxiety. It is an organ especially suited for the demonstration of both psychosomatic and somato-psychic relationships. Attention is focused on its close relationship to life and many associations and conditionings readily take place as a result of this identification. Certainly, the capacity of the individual to carry on a useful and happy life is possibly more often closely related to his psychic evaluation of his cardiac condition than to the actual organic state of his heart. This is true both with regard to heart disease associated with structural change and to psychically induced functional cardiac disturbances.

Disturbances in Rate and Rhythm

Changes in cardiac rate and rhythm occurring in psychological situations provoking fear, anxiety, *etc.*, are sufficiently obvious to require only that they be mentioned. Large numbers of men were rejected for military service because of tachycardia. In many, a rather definite pattern of development was noted: (1) an overprotective mother; (2) an inci-

dent directing attention to cardiac function; (3) examination of cardiac function; (4) the inference that cardiac disease is present through statements made by the physician or suggested by restricting the activities of the patient; (5) maintenance of a dependent position with regard to mother or other members of the family; and (6) an examination leading to a reawakening of fear relative to self through possible death threats or anxiety over the possible absence of a cardiac condition which would require a less dependent relationship. Decreased cardiac rate in states of melancholia are a common finding and probably, in addition to being evidence of a slowly functioning organism, may be related to the patient's desire to die. Rhythm disturbances, extrasystoles, paroxysmal tachycardia, *etc.* are frequent expressions of altered emotional tones. Attacks of paroxysmal tachycardia can readily be precipitated by emotionally exciting incidents. No small importance should be placed on the usefulness of these symptoms as a means of obtaining secondary gains. The objective nature of the symptoms enables the patient to be dependent when he desires dependence, to get sympathy when sympathy is needed, and to avoid frustration by having others excuse his failures. I recall a soldier who attempted to use his paroxysmal tachycardia, which he felt had an organic basis, to find relief from a situation that he found rather disturbing. Failing in this, he ceased to express his frustrations in a symptom which had no secondary gain value.

Syncope

Collapse following fantasied, consciously anticipated, or experienced trauma or other emotional stress is one of the more dramatic expressions of cardiovascular psychosomatic changes. An etiologic relationship may be found in such inciting incidents as venipuncture, anticipated injury, actual injury, and surgical procedures. Such incidents act as initiating fac-

* Professor and Chairman, Department of Neurology and Psychiatry, The Chicago Medical School; Associate Attending, Mt. Sinai Hospital; Attending Neurologist, Cook County Hospital.

tors, but once initiated the characteristic symptom complex may follow any emotional stress. The psychopathologic cause is believed to be chronically repressed or unrelieved emotional stress. The physiologic response to the emotional stress provides a defense against a fantasied injury. The organism, being unable to build any strong defenses against mobilized aggressive feelings or to situations threatening mutilation, may respond with vasodepressor syncope as a means of resolution of such conflicts when such a physiologic mechanism has previously been initiated as a mode of reaction. The symptoms are primarily those of a vasovagal reaction with concomitant sympathetic stimulation in an attempt to restore the balance. Weakness, dizziness, pallor, sweating, sighing respiration, nausea, fall in blood pressure, and bradycardia or tachycardia are characteristic symptoms. Loss of consciousness may occur or may be prevented by assuming the recumbent position. Change to a vertical position before complete recovery results in a return of the symptoms. Convulsive movements may occur if the recumbent position is not assumed at all or if such a position is not taken shortly after the onset of symptoms. Recovery of consciousness is rapid, in 20 to 40 minutes.

Angina Pectoris and Coronary Disease

The clinical entities of angina pectoris and coronary disease are increasing in frequency, especially in highly competitive societies. The mounting incidence of these clinical syndromes being reported in women might be a reflection of the increasing competitiveness of women in our society. Although the psychological causative factors have not been adequately worked out with regard to thrombosis and angina, it has been reported that hostility, aggressiveness, and competitiveness are important underlying psychopathological phenomena. In a report by the Menningers, cases are cited in which strong attachments to the father existed, with obliteration of hostile feelings toward the father because of these strong attachments—a psychological defense mechanism known as identification with the aggressor. The identifica-

tion with the father who, in each case, had heart symptoms, was probably motivated by the guilt feelings engendered by unconscious hostility. The hostile feelings toward the father are intolerable and therefore are repressed. The guilt feelings created by the hostility are then converted into the oft expressed idea "you deserve to suffer in the same way he does." The secondary factors of implications by physicians and others and the anxiety with regard to organic disease all tend to the development of further symptoms.

Neurocirculatory Asthenia

The whole concept of neurocirculatory asthenia has undergone considerable revision since the first World War. In many instances formerly classed as organic heart disease, the tendency in the second World War was to place this response in its proper category among the disturbances of psychological equilibrium. The effort syndrome is rather obviously an anxiety neurosis in which emphasis has been placed on the cardiac manifestations. The actual diversity of symptoms found is noted in the following positive symptoms found in a study of a group of patients suffering from Da Costa's disease:

- | | |
|------------------------|---------------------------|
| 1. Fatigue | 8. Breathlessness |
| 2. Nervousness | 9. Sweating |
| 3. Palpitation | 10. Dizziness |
| 4. Vascular throbbing | 11. Trembling, shakiness |
| 5. Syncope | 12. Thoracic pain |
| 6. Paresthesias | 13. Dry mouth |
| 7. Headaches, insomnia | 14. Vomiting and diarrhea |
| nightmares, phobias | 15. Nocturia |

Such signs as the following are quoted:

1. Typical facies
2. Nervous manner
3. Overactivity in heart and visible vessels
4. Tachycardia
5. Slight blood pressure rise
6. Cold, blue hands
7. Visible flushing
8. Hyperpnea
9. Frequent sighing
10. Palmar and axillary sweating
11. Tremor
12. Poor physical development

It has been customary to diagnose neurocirculatory asthenia on the basis of "the elimination of an organic disease." In some instances, the actual presence of organic findings may lead to confusion as to the important causative factors in the symptom formation. A good psychiatric history will usually reveal a pattern of anxiety, insecurity, and dependence which antedated the beginning of the difficulty. A series of clinical impressions have occurred to me which suggest these factors as being significant in the development of neurocirculatory asthenia: (1) a basic personality structure in which environmental factors have led to feelings of extreme insecurity about possible death or mutilation; (2) the parents are often invalidated by neuroses or cardiac pathology, or they show an extreme concern over possible injury to the child; (3) statements implying the presence of cardiac disease, actual illness, especially prolonged illness leading to extreme dependence—usually on the mother, and fear of losing the person upon whom dependence is placed form a substrata of psychological preparation; (4) some incident, illness, or other factor which might direct attention to the heart is introduced and is then reinforced by statements made by physicians; (5) the attitude of the parents to overprotect and to restrict activity tends to firmly establish the heart as an organ of inferior quality; (6) anxiety manifestations induced by external or internal happenings are thereafter noted by their physiological concomitant of tachycardia; (7) the appreciation of the tachycardia produces a reinforcement of the idea that the heart is diseased and further anxiety is engendered; and (8) situations associated with increased rate or which produce anxiety about findings referable to the heart become the basis for immediate reawakening of symptoms. The physical examination, with its threat to the possible reaffirmation of the presence of disease or its threat to the removal of a dependent situation, is especially provocative.

The role of the various factors mentioned in the development of a cardiac neurosis is emphasized by a case seen

recently. The patient had been a cardiac invalid for years and had spent a considerable part of her last ten years under medical care. Her chief complaints were referable to the heart and were characterized by symptoms of the effort syndrome occurring periodically. The history revealed the birth of a child with a congenital heart lesion. The patient recalled being slightly injured while at a race track during pregnancy. Feelings of guilt about her possible role in the causation of the heart lesion in the child were uncovered, with emphasis on her failure to be more protective of her pregnancy. The child was protected to the utmost and constant psychic conditioning with regard to the heart occurred during the child's life, which terminated in another situation which was guilt-provoking to the patient. Considerable hostility was repressed and was replaced by the need for excessive care of the child. This resulted in restriction of the mother's life. The guilt provoked by the situations mentioned and the repressed hostility acted, along with identification with the child, as the basis for the occurrence of anxiety attacks in which the cardiac expression was particularly recognized.

Hypertension and Hypertensive Heart Disease

The problem of hypertension has received new interest of late because of the findings of Goldblatt, indicating the relation between hypertension and renal ischemia. A summary of the pathogenesis of hypertension would include the following as important factors:

- (1) Renal parenchyma pathology
 - (a) Glomerulonephritis
 - (b) Urinary obstruction
 - (c) Polycystic kidneys
 - (d) Pyelonephritis and others
- (2) Nervous system
 - (a) Conditions with increased intracranial pressure
 - (b) Diseases of the brain stem
- (3) Endocrine System
 - (a) Pituitary basophilism
 - (b) Adrenal and ovarian tumors
- (4) Arterial vascular disease
 - (a) Obstructive arteriosclerosis of renal vessels

- (b) Coarctation of the aorta
(5) Essential hypertension

Luisada suggests the simple classification of

- (a) Secondary hypertension
(b) Essential hypertension

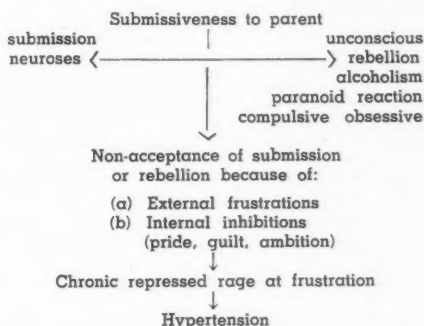
It would seem that there are intrinsic hereditary and constitutional factors responsible for vascular hypertonus. To this may be added a factor of psychic vasoconstriction which is sufficient to start the manifest symptoms or to accentuate them if they already exist. Fishberg's view with regard to the psychic role in hypertension is quoted as follows: "In all probability, emotional and mental strains play purely an accessory role in the genesis of hypertension, serving to precipitate and aggravate the increase in blood pressure in those individuals who have the inherited constitutional predisposition."

Discussion

The previous discussions have thus far demonstrated a relationship between psyche and soma which, in the case of the cardiovascular system, manifests itself in rate and rhythm disturbances and in a syndrome of psychic and physiologic symptoms which may seriously incapacitate the individual. Hypertension and hypertensive heart disease further emphasize the mind-body relationship in the development of structural changes related to psychic disturbances. Essential hypertension as a disease in which no cardiac, renal, or vascular disease precedes the hypertension, is probably one of the gravest disease processes in middle life. Studies in countries where the impact of industrial and civilization tensions have not been felt as yet show that the population generally has a much lower incidence of essential hypertension than in the countries in which civilization has advanced rapidly. The Negro has shown an especially significant rate of hypertension in this country as opposed to an absence of essential hypertension in the African Negro. The significance of this trend in the American Negro is especially interesting in light of the recent developments with regard to focal emotional conflicts. That rage, anger, and fear are associated with

blood pressure elevation is established physiologic knowledge; the findings of muscle tension, smooth as well as skeletal, noted by Dunbar in patients with essential hypertension, is common clinical knowledge. The interpretation placed on such a state of muscular tension, "an attempt to inhibit and a defense against both actual and fantasied situations leading to chronic rage," is not common knowledge. The dreams of hypertensives are frequently in the nature of life-threatening situations, again evidence of their aggressive impulses.

Psychoanalytic investigation suggests that hostility and resentment resulting from inadequate solution of conflict situations produce a chronic repressed rage state which manifests itself as a chronic physiologic overaction which eventually leads to structural changes. Conflict situations are not provocative of a blood pressure rise if a solution is obtained by passive acceptance of a frustrating situation, working through the conflict, neuroses, or some other mechanism. The hostility in patients developing hypertension is close to the surface and the patient is literally trying to hold his blood pressure down. On the surface, gentility and a very pacific attitude often characterize the patient. The work of Saul, Alexander, Draper, and others, although based on a small group of hypertensive patients, can be diagrammed as follows:



As Alexander has indicated, hypertension is a disease of civilization. Civilization is uniquely conducive to the development of hostility and rage, but it

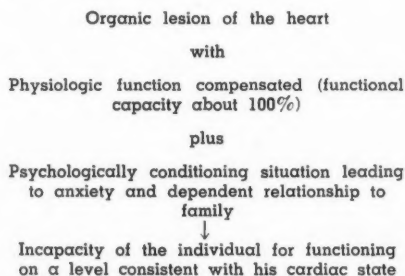
likewise demands a high degree of repression, leading to a persistence of and accumulation of aggressivity.

The symptoms supposedly commonly associated with hypertension have been studied by me clinically for several years. Headache, vertigo, ringing in the ears, precordial distress, and tachycardia are symptoms which are frequently ascribed to the hypertensive state. It is my impression as well as that of Weiss, *et. al.*, who studied a group of hypertensive patients physically, by laboratory methods, with Rorschach tests, and through laboratory interviews, that these symptoms are an expression of the concomitant psychological disturbances. My impression is that the physiological hypertensive state and symptoms which are referable to structural alterations occur when a breakdown in the compensation of brain, heart, kidney, *etc.* occurs. Symptoms usually ascribed to the hypertension are most frequently those which express rage, inhibition of rage (*e.g.* weakness), or the reaction to fantasied body changes which express the need for punishment on the basis of the Talion principle.

A great deal of emphasis is commonly placed upon the factors of murmurs and the problems of decompensation. A careful investigation of the problem will reveal that a very large number of individuals are, for practical purposes, not impaired functionally by the appearance of organic heart disease. Several possibilities exist with regard to organic heart disease and its symptoms. Organic damage may be such that compensatory mechanisms can adequately care for the patient's partial incapacitation so that normal functions may be carried on throughout life without any awareness

of a disability existing on the part of the patient. Secondly, the individual may be unable to be effectively maintained in a compensated state except by restricting his activities. He may develop a fear of threat to life with diminished ability for adaptation based on psychological overlay. Statements of a physician may make an individual, whose adaptive capacities are excellent, become a confirmed invalid. An individual of authority has indicated to the patient that a threat to his existence is present and has set up a train of associative phenomena leading to fear, anxiety, tachycardia, hyperhidrosis, *etc.* These symptoms bring about a certain amount of increased attention from relatives, with a certain amount of protection and assurance of protection that goes with such a relationship.

Diagrammatically the relationship is about as follows:



It should always be the physician's aim to adequately investigate the psychological situations, events, and stimuli which may have been important in the development of personality structure and which may have acted to predispose, to perpetuate, or to precipitate the cardiovascular disfunctions which bring the patient to him.

INFECTIOUS MONONUCLEOSIS

ISRAEL DAVIDSOHN, M.D.*

Infectious mononucleosis is of interest to the clinician, internist, pediatrician, clinical pathologist, hematologist, serologist, and even to the medical historian.

There are several special reasons for its appeal to the historian. In the case of most diseases, it is impossible to state when they became recognized as distinct entities. Infectious mononucleosis is one of few about which one can say with a reasonable degree of assurance when it made its debut. Its origin is traced to a paper by a Viennese pediatrician, Emil Pfeiffer, given at the German Congress of Medicine at Wiesbaden in 1889¹.

The disease presents another interesting feature for medical historians in that it illustrates the multicentric origin common to many medical discoveries. Careful study of medical history has shown the frequency with which the same idea was generated simultaneously in the minds of several investigators. When Pfeiffer presented his paper, Heubner, the noted German pediatrician, stated in the discussion that he had seen cases of the same kind at least since 1879. Still another person had made apparently similar observations. The Russian professor of pediatrics, Filatow, described the disease without knowing of Pfeiffer's report. He did not write a paper on it but in his lectures to students he gave a complete description and called the condition "idiopathic benign swelling of lymph nodes". One of the students edited Filatow's lectures and in it the description has been recorded. Pfeiffer coined the name *Dru-sen-fieber*, glandular fever.

Sprunt and Evans have usually been given credit for the description of the characteristic hematologic changes². They thought that they were describing an entirely new disease entity and used a

different term for it—infectious mononucleosis. Actually, the credit for the first description of the hematologic findings belongs to Burns³. Even the term infectious mononucleosis was used by Baetjher in 1915—before Sprunt and Evans used it.

The history of infectious mononucleosis demonstrates also the influence of developments in the laboratory on clinical medicine. After Pfeiffer's publication, the disease became well known on the continent of Europe and in England. This recognition was based mainly on the clinical description by Pfeiffer. History has shown that whenever the recognition of a disease is based exclusively on clinical criteria, its identity has a tendency to become vague due to inclusion of cases of a different nature. This was also the case with infectious mononucleosis. Cases began to be reported which had only a superficial resemblance to the disease. As a result, the term glandular fever became discredited. Between 1900 and 1920 relatively little about it appeared in the literature.

Two papers dealing with the characteristic blood changes must be given credit for re-awakening interest in the disease in the United States and in England, *viz.*, the already mentioned paper by Sprunt and Evans in this country and one by Tidy and Morley in England⁴. Another powerful stimulus to the recognition and identification of the disease was given in 1932 by Paul and Bunnell, who discovered specific serologic changes in the blood⁵.

The history of infectious mononucleosis can thus be divided into the following periods: (1) 1889 to 1900, the decade immediately following Pfeiffer's announcement of the new entity; (2) 1900 to 1920, the period of obscurity due to progressive loss of identity; (3) 1920 to 1931, the hematologic period; and (4) 1932 to the present, the serologic period, dating back to Paul's and Bunnell's introduction of the serologic test. The serologic period can be further subdivided

*Professor and Chairman, Department of Pathology, The Chicago Medical School; Pathologist and Director of Laboratories, Mt. Sinai Hospital; Director, Mt. Sinai Medical Research Foundation; President, American Society of Clinical Pathologists.

into the early phase, which was initiated by Paul's and Bunnell's recognition of the characteristic heterophilic antibodies, and the later one which followed the identification of antibodies specific for the disease by the introduction of the differential test⁶. Finally, a better understanding of our knowledge of the disease has been achieved by extensive pathologic studies on various tissues giving us a new concept of the changes produced in the body.

There is another interesting feature of the disease, which, at first glance, appears to be determined by geography, but actually is due to social factors. In England, most published cases resembled the type described by Pfeiffer: mostly in young children, particularly in boys of 8 to 14 residing in preparatory schools. In the United States, the disease has been observed mainly in college students from 18 to 24 years of age. Epidemics and sporadic cases have been common here and in England. On the other hand, in Continental Europe, mainly sporadic cases have been observed. These differences are explained by the existence of preparatory schools in England with boys attending them, and of colleges in the United States with the students living in dormitories, whereas in Continental European dormitories are less popular.

Infectious mononucleosis occurs in various forms and under various disguises. Many attempts have been made to classify it into definite and distinct groups. Tidy's division into four groups seems most satisfactory⁷: (1) The form which most closely resembles glandular fever as described by Pfeiffer, with fever, rapid and visible swelling of cervical lymph nodes, and a short duration. The lymph nodes are frequently tender in this form of the disease.

(2) The disease, occurring in adolescents and young persons, with a longer course, less pronounced swelling of lymph nodes and, usually, milder fever.

(3) The third variety, which was studied particularly thoroughly in Germany, with ulcerative and membranous lesions in the pharynx which are commonly invaded by the micro-organisms seen in Vincent's Angina, is frequently difficult

to distinguish from diphtheria. It is this form of the disease which the German writers called lymphocytic or monocytic angina. They made the mistake of assuming that it is a constitutional reaction to an infection in which one person reacts with an increase of lymphocytes, a second with an increase of monocytes, and a third with an increase of polymorphonuclear leukocytes. They placed the emphasis on the constitutional reaction of the host and not on the infectious agent.

(4) The last form has a long febrile course, somewhat resembling typhoid fever, frequently with a long period of prodromal manifestations, and with lymph nodes appearing late in the disease—sometimes two or three weeks after the onset of symptoms. The enlargement of lymph nodes in this form is not very striking.

This classification is useful, but it should be kept in mind that the disease is a single entity and that there are many transitions and modifications in the scheme as it is outlined.

Until recently, writers on the subject have been emphasizing the benign nature of the disease. During the last few years, a rather impressive number of fatal cases have been described so that the disease is not to be considered as absolutely benign as it has been. Nevertheless, the serious complications are still rare. Therefore, it seems justified to quote the old saying that infectious mononucleosis interests us not for what it is but for what it pretends to be. This statement is an expression of the fact that the disease imitates many other clinical entities.

Infectious mononucleosis can thus be defined as an acute infectious disease of the reticulo-endothelial tissues, especially of the lymphatic tissues, with fever, generalized swelling of lymph nodes, characteristic changes in the white blood cells and in the blood serum, and leading, as a rule, to recovery within a few weeks.

THE CLINICAL PICTURE OF INFECTIOUS MONONUCLEOSIS.

The onset of the disease is vague. There is an incubation period varying from 4 to 28 days. In the fully developed

disease there is fever (varying from mild to 104° F. and occasionally going as high as 106° F.), chills, sweats, headache, dizziness, malaise, retro-orbital aching, irritability, and asthenia—all of varying severity. Cases without fever occur, especially in epidemics.

Lymph nodes usually become involved early in the disease. The cervical lymph nodes are the first to be enlarged, frequently beginning on one side and spreading to the other side and to other regions of the body. Their enlargement may appear simultaneously with the onset of fever, or it may precede or follow it. The enlargement appears very rapidly, which is the probable explanation of the characteristic tenderness.

The tenderness should be looked for because it is frequently of help in the differential diagnosis. Occasionally, the tenderness of lymph nodes in the back of the neck is sufficiently pronounced to force the patient to hold the neck rigidly and invite the suspicion of meningitis. The enlarged lymph nodes may persist for a long time, sometimes in all regions, sometimes only in one location. Suppuration is a rare complication.

The most important feature of infectious mononucleosis is the frequency with which it is mistaken for other diseases. This is well illustrated in our own material. During the last 16 years we studied about 219 cases of infectious mononucleosis. Some of these were sent only for laboratory tests and complete clinical data was not available. Clinical data was known in 106 cases. In these cases, experienced clinicians made the correct diagnosis in 43 cases before the blood counts and serologic tests were available. In the remaining 63 cases, 26 different diagnoses were made. In addition, 23 other diagnoses were collected from the literature⁸. The diagnostic difficulties are not at all surprising when one considers the variety of clinical manifestations. It is worth noting that in almost 5 per cent of cases there was no noticeable enlargement of lymph nodes, and that in almost 13 per cent of cases there was no record of fever. The form which involves the pharynx with extensive membrane formation is the one

which gives rise to differential diagnostic difficulties with diphtheria.

The incidence of splenomegaly was less in our series than has been reported in the literature. Some of this difference may be attributed to individual variations in the ability to elicit a slightly enlarged spleen. In view of reported cases of ruptured spleens in the course of vigorous palpation, it may well be that less effort to palpate the spleen is in the patient's interest. The pain in the upper abdomen is frequently due to a tender and rapidly enlarging spleen. In one of our cases the pain was so severe that an operation was prevented only by the laboratory report. Pain in the right lower abdomen has probably been responsible for the removal of appendixes. It is due to rapid enlargement of lymphatic tissue in the appendix and to swelling of mesenteric lymph nodes.

The headache is sometimes pronounced, particularly when retrobulbar. There may be marked prostration lasting for many weeks.

Various skin rashes have been described resembling those seen in exanthemata. They may be scarlatiniform or morbilliform. Purpura with hemorrhages from various parts of the body have been noticed. Icterus is a rare complication, occurring most frequently in adults. The changes in the liver, to be described later, explain the jaundice. Intestinal manifestations in the form of diarrhea and emesis are also a part of the picture, as is gingivitis.

The occasional non-specific positive serologic tests for syphilis are interesting. Their nature is not known. It is readily seen that a combination of a skin rash, enlarged lymph nodes, and a positive test for syphilis may lead occasionally to unnecessary therapy. In our own material the incidence of positive tests for syphilis was much lower than has been reported in the literature.

In connection with the puffiness around the eyes, which is caused by swelling of retro-bulbar tissue, it is interesting to note that in a recent report, non-specific positive precipitin tests with trichina antigen were reported in patients with infectious mononucleosis⁹.

BLOOD IN INFECTIOUS MONONUCLEOSIS

The red cells and platelets are not altered. Early in the disease there is an increase of leukocytes with a shift to the left. The latter is present even when there is no leukocytosis and in the occasional cases of leukopenia. The changes in the myeloid cells are definite only early in the disease. They are followed usually by transient increase of monocytes. Eosinophils are decreased early in the disease and are raised in convalescence.

The most important alterations are quantitative and qualitative changes in lymphocytes, which can be classified under the following headings:

(1) Hyperplasia. An increase in the number of the cells ranging from 15,000 to 25,000 in most instances, although rises to 40,000 in adults, and to 70,000 in infants, have been reported. An increase beyond these figures should make one suspect another condition.

(2) Hypertrophy. In most instances the lymphocytes are larger than the normal cells. Striking differences in size are frequent (lymphocytic anisocytosis).

(3) Nuclear pleomorphism. There is loss of the normal oval or round shape with formation of irregular lobes (lymphocytic poikilocytosis). The chromatin is clumped, dense, and lacks the differentiation seen in normal lymphocytes. In some cells the nuclei resemble those of monocytes (monocytoid deviation). Occasional nuclei may show anaplastic changes with prominent nucleoli. Division of nuclei and mitotic figures may be present.

(4) Cytoplasmic basophilia. The cytoplasm is abundant, usually deeply basophilic, and sometimes vacuolated (vacuolar degeneration).

The mononucleosis persists for weeks and, in some instances, even for months. In occasional cases, abnormal lymphocytes may be found years after the illness.

The morphologic changes in the blood are not pathognomonic for infectious mononucleosis because similar cells may be found in other conditions.

CEREBRO-SPINAL FLUID

The pressure is usually slightly increased. There is pleocytosis, as a rule, with less than 200 cells, but cases have been reported where the cell count was up to 1000, consisting entirely of lymphocytes. A slight increase of globulin has also been reported.

URINE

Except for the occasional cases of renal lesions or of renal manifestations of purpura, the only finding is a trace of albumin.

LIVER FUNCTION TESTS

We found an elevated icterus index, in most instances in the range of so-called latent jaundice, in more than 50 per cent of cases. The cephalin flocculation test is frequently, and the thymol turbidity test is uniformly, positive. Cholesterol and cholesterol esters are within normal limits. This is in keeping with recent reports on liver function studies in infectious mononucleosis by other writers.

THE SEROLOGIC DIAGNOSIS OF INFECTIOUS MONONUCLEOSIS

There are two serologic tests for infectious mononucleosis. The so-called pre-

TABLE 1
The Presumptive Test for Infectious Mononucleosis

Technic	
The physician:	Obtain 5-10 cc. of blood under aseptic precautions. Send to the laboratory.
The laboratory:	(1) Reagents: (a) Serum inactivated for 30 minutes at 56° C. (b) 2% suspension of sheep red cells.
	(2) Procedure: To 0.25 cc. of increasing dilutions of serum, add 0.1 cc. of the sheep cell suspension.
	(3) Reading of results: LET STAND AT ROOM TEMPERATURE FOR 2 HOURS OR LESS. If in a hurry, read test after 15 minutes, and if negative, repeat reading at intervals. In many instances positive findings can be obtained after these short periods of time. The titer is the reciprocal value of the highest serum dilution still showing agglutination.

sumptive test, also known as the heterophile antibody or Paul and Bunnell test, and the differential test.

The technic of the presumptive test is very simple. It is presented in outline form in Table 1. The history of this test goes back to my studies on heterophilic antibodies in serum disease published in 1929¹⁰. I reported at that time that persons who are given horse serum or horse immune serum develop an elevated titer of antsheep agglutinins, especially if they had serum disease. Natural antsheep agglutinins are present in about 93 per cent of persons. The titers vary from 1:7 to 1:112. The range, in close to 90 per cent, is from 1:7 to 1:28; the titers 1:56 and 1:112 are rarely present. In those given horse serum, titers of a very high order may be found.

This observation was the outcome of the study of the so-called Forssman antigen and antibody. Forssman described, in 1911, an antigen, in tissues of the guinea pig, capable of producing antsheep hemolysins when injected into rabbits. Later the same substance was found distributed widely in many animal species and in some bacteria. The phenomenon, when first announced, created a considerable stir in the circles of immunologists because it was not in agreement with the prevailing opinions regarding the specificity of the antigen-antibody relationship. It was unusual and unexpected to find that, following injection into rabbits, for example, of guinea pig kidney suspensions, powerful antibodies developed against red blood cells of sheep, an animal species only distantly related to the guinea pig. Still greater was their consternation when entirely unrelated antigens (*e.g.*, suspensions of pneumococci), were found to possess the same property of producing antsheep hemolysins. At present we are not puzzled, because we know that antigens are chemical substances that can be distributed by nature without regard to zoologic relationship. The guinea pig is particularly rich in the Forssman antigen and therefore has been selected as the representative of carriers of the Forssman antigen, which are placed in the so-called guinea-pig group. The rabbit represents animals free of the

Forssman antigen, the rabbit group. In some animals, as in the guinea pig, the antigen is present in the tissues but absent from the blood. In others (sheep), it is present in the blood and absent in the tissues. In others again (birds), it is present in the tissues and in the blood. The horse has Forssman antigens in the tissues as well as in the serum. Man has the antigen in red cells which have the factor A.

The antsheep agglutinins and hemolysins which develop following injection of horse serum are due to the presence of the Forssman antigen in horse serum. Their Forssman nature has been further confirmed by the fact that addition of guinea pig kidney suspension to human serum removes the antibody. Interestingly, the natural antsheep agglutinins, present in over 90 per cent of persons, are also of the Forssman type because they too are removed by additions of the Forssman antigen.

The resemblance existing between certain manifestations of serum disease and of acute rheumatic fever prompted Paul and Bunnell to check my results. They were able to confirm them by finding that an elevated titer of antsheep agglutinins was present only in patients who had been treated with horse serum. However, they found three cases which were exceptions. They had elevated titers though they had never received horse serum in any form. They had, in common, clinical manifestations of infectious mononucleosis. That is what led them to the brilliant conclusion that an elevated titer of antsheep agglutinins may be used as a diagnostic test for infectious mononucleosis.

Paul and Bunnell used in their work the technic which I had originally employed for my studies on serum disease. This technic calls for overnight incubation in the icebox. In order to simplify and shorten the test, I described a technic which makes it possible to read the test in two hours or less¹¹.

The heterophile antibody test or the Paul and Bunnell test has definite limitations. It is purely quantitative because antsheep agglutinins are present also in persons free of infectious mononucle-

osis, in perfectly normal individuals, and in persons suffering from a variety of diseases. The only thing that is different in infectious mononucleosis is the elevated titer. On the other hand, as will be shown later, many patients with infectious mononucleosis have titers lower than the highest normally seen (1:112). Another difficulty arose from the fact that whenever a patient was given an injection of horse immune serum because diphtheria or another disease requiring serum therapy was suspected, the problem of differentiation between serum disease or serum sensitization and infectious mononucleosis could not be solved merely by employing the test for heterophilic antibodies. These considerations prompted me to investigate the problem.

The first question that had to be answered was whether the antsheep agglutinins in infectious mononucleosis are of the Forssman type. They were not removed by guinea pig kidney suspension. This observation established the basis for the differential test by showing that the agglutinins for sheep red cells in the serum of patients with infectious mononucleosis are not of the Forssman type. This is how the differential test came to be.

These preliminary remarks will facilitate the interpretation of results of the presumptive test, recorded in Table 2. The principle of the differential test is described in Table 3. The interpretation of the differential test is summarized in Table 4. Almost 16 per cent of patients

TABLE 2
Interpretation of the Presumptive Test for Infectious Mononucleosis

In the presence of clinical and/or hematologic findings suggestive of infectious mononucleosis, titers of 1:224 or higher in the presumptive test confirm the diagnosis of infectious mononucleosis. If the titer of the presumptive test is less than 1:224 in the presence of clinical and/or hematologic findings suggestive of infectious mononucleosis; or, if the titer of the presumptive test is 1:224 or higher in the absence of clinical and hematologic findings suggestive of infectious mononucleosis; or, if the patient has a history of a recent horse serum injection, the result of the presumptive test should be checked by the differential test.

TABLE 3
Principle of the Differential Test for Infectious Mononucleosis

The heterophilic antibodies (antsheep agglutinins) in infectious mononucleosis are not of the Forssman type. They are not absorbed by suspensions of guinea-pig kidney but are readily and completely absorbed by beef red cells. The heterophilic antibodies in normal persons, in horse serum sensitization, and in a variety of other conditions, are of the Forssman type and are readily and completely absorbed by suspensions of guinea-pig kidney. In horse serum sensitization, absorption with beef cells removes the sheep agglutinins readily and completely, whereas in normal persons and in patients with diseases other than infectious mononucleosis or horse serum sensitization, sheep agglutinins are frequently removed only partially by the beef cell antigen.

TABLE 4
Interpretation of Results of the Differential Test for Infectious Mononucleosis

In no instance of infectious mononucleosis, in our experience, were agglutinins for sheep red cells removed completely by guinea-pig kidney. Maximum absorption was 87.5 per cent, which is equivalent to a three-tube-drop of the titer. This was seen in only 10 per cent of the tests.

If all or almost all (more than 90 per cent) of the agglutinins have been removed in the differential test, infectious mononucleosis is excluded.

In our experience, infectious mononucleosis is the only disease in which antsheep agglutinins show the following behavior:

(1) At least 12 per cent of the original titer of antsheep agglutinins remains after absorption with guinea-pig kidney;

(2) The antsheep agglutinins are completely removed after absorption with beef red cells.

Examples

Presumptive Test	Titer of		Result
	Guinea Pig Kidney	Differential Test After Ab- sorption With	
		Beef Red Cells	
(b) 1:448	1:224	1:224	NEGATIVE for infectious mononucleosis
(c) 1:448	1:224	0	POSITIVE for infectious mononucleosis
(a) 1:224	0	1:112	NEGATIVE for infectious mononucleosis

in whom the presumptive test (Paul and Bunnell) was done early in the disease showed titers less than 1:112, a non-diagnostic titer. In follow-up tests, from 3 to 18 weeks after onset of symptoms, 38 per cent had titers of 1:112 or less. In other words, in 56 per cent of cases the Paul and Bunnell test was not diagnostic. The specific serologic diagnosis was made possible only through the differential test.

When does the differential test become positive? The test may be negative for two weeks and become positive later. It may happen that the presumptive test is negative although the differential is already positive. This showed the necessity of doing the differential test in spite of low or borderline titers and of repeating the test until at least the third week of disease.

When does a positive test become negative? In our experience the intervals varied from 6 to 38 weeks after onset of the disease, but even with complete disappearance of clinical manifestations the antibodies characteristic for the disease may persist for at least as long as 18 weeks.

STUDIES ON SUGGESTED MODIFICATIONS OF TECHNIC

In the course of time, since the presumptive and differential tests were published¹², various modifications have been suggested, most of them aiming at shortening the time factor or simplifying the technic. The oldest of these suggestions is the introduction of centrifugation as a means of speeding up the reaction—a method which has its merits. However, it must be kept in mind that it not only accelerates the reaction but intensifies it as well, so that entirely new control values for the upper normal titers have to be established. It is definitely more time-consuming because the centrifugation of a row of from 8 to 12 tubes, the labeling of each tube, and the other steps required by centrifugation are certainly not simpler than leaving the tubes at room temperature for two hours, especially since the test tube technic permits reading of results, whenever speed is indicated, after shorter incubation periods. The two-hour waiting period is the maximum time needed for a final report in a

negative case. In positive cases, reading of results after 15 or 30 minutes of incubation will frequently permit an earlier report. Even the maximum waiting period of two hours is rarely an important factor in infectious mononucleosis. We have reported recently that the absorption in the differential test is almost instantaneous¹¹. This has further shortened the time needed for the test.

PATHOLOGIC LESIONS IN INFECTIOUS MONONUCLEOSIS

Recent autopsy studies¹ have increased our knowledge of pathologic tissue changes in infectious mononucleosis. Custer and Smith published a most satisfactory review of this knowledge based on their studies of biopsy and autopsy material¹³. The illustrations are the best available on the subject. They explain the reported disturbances of liver function, the roentgenologic findings of pulmonary consolidation, the neurologic manifestations, and many other findings.

Here, I should like only to discuss the microscopic changes in the spleen as a means of correlating certain clinical manifestations and hematologic findings with anatomic changes.

Microscopic sections of the spleen show a transformation of the splenic parenchyma by a diffuse replacement with cells, many of which resemble, morphologically, the lymphocytes seen in the peripheral blood.

Two lesions are especially interesting. One of them is the infiltration of the capsule together with the trabeculae by the abnormal lymphocytes leading to what Custer and Smith call "dissolution" of the connective tissue in these supportive structures. When one sees these changes on a microscopic section one understands readily why a minimal exertion, such as the act of defecation or slight pressure in the course of an attempt to palpate the spleen, may cause rupture.

Another interesting feature is the presence of massive subintimal infiltration in the veins with these abnormal lymphocytes. In some sections, the borderline between the subintimal infiltrations and the contents of the lumen is obliterated. This breakdown of the tissue-blood bar-

rier is seen everywhere in the lymphoid tissue, but nowhere can it be demonstrated quite so readily as in the blood vessels of the spleen. This finding permits the interpretation that these abnormal lymphocytes are tissue cells, tissue lymphocytes, which find their way into the circulation because the barrier between tissues and the circulation has been obliterated.

Subintimal accumulations of hyperplastic cells are not at all uncommon and certainly not limited to infectious mononucleosis. A case of lymphatic leukemia was studied by me recently in which, in the course of the patient's life, cells were found with nuclei which were atypical in appearance. Some of them were split in two and presented the changes which have been frequently described as characteristic for lymphosarcoma cells. On the basis of clinical and hematologic observations, the diagnosis of lymphosarcoma was made. The lymphosarcoma cells were not permanently present in the course of the disease of this patient, who was under prolonged clinical observation. Days and weeks during which they were present alternated with periods in which they were absent. When the patient expired, sections from the spleen, kidneys, and lungs showed subintimal infiltration in veins similar to those seen in patients with borderlines between the intimal lining and the lumen and its contents obliterated. This finding suggested the explanation of the presence of cells resembling lymphosarcoma cells in the peripheral circulation. It is reasonable to assume that there is a barrier between the tissue and the peripheral blood through which lymphocytes, even in lymphocytic leukemia, have to pass before they are permitted to get into the circulating blood. The existence of such a barrier is suggested by the fact that there are aleukemic leukemias. It is possible that a certain degree of maturation of some kind has to be achieved before a white blood cell is permitted to leave the tissues and enter the circulation. The existence of subintimal infiltrations, as in the case just quoted, may make it possible to pass that barrier without the necessary matur-

ation of the cell, merely due to the accidental localization of the leukemic or infectious mononucleosis type of infiltrations.

The extensive tissue changes in infectious mononucleosis in some early cases suggest that they are probably fully developed early in the disease. On the other hand, the development of positive serologic changes late in the course of the disease suggests the possibility that the serologic changes may follow the tissue changes. This seems a reasonable conclusion on the basis of available evidence. It is further supported by the fact that the characteristic lymphocytes are found in the blood early in the disease, with only rare exceptions. At least in our experience, we have not seen a case with a normal differential blood picture at a time when the serologic test was positive. The concept that the abnormal lymphocytes are cells which enter the circulation because of the lifting of the barrier between the tissues and the peripheral blood makes it necessary to place the tissue changes early in the disease, certainly at a time when the patient manifests clinical signs of the disease and when abnormal blood cells are present.

REFERENCES

1. Pfeiffer, E.: *Jahrb. f. Kinderheilk.*, 29:257, 1889.
2. Sprunt, T. P. and Evans, F. A.: *Bull. Johns Hopkins Hosp.*, 31:410, 1920.
3. Burns, J. E.: *Arch. Int. Med.*, 4:118, 1909.
4. Tidy, H. L. and Morley, E. D.: *Brit. M. J.*, 1:100, 1921.
5. Paul, J. R. and Bunnell, W. W.: *Am. J. M. Sc.*, 183:19, 1932.
6. Davidsohn, I.: *Am. J. Clin. Path. (Tech. Suppl.)*, 2:56-60, 1938.
7. Tidy, H.: *Infectious Mononucleosis*. George R. Minot Symposium On Hematology. Edited by Dameshek and Taylor. Grune and Stratton, 1949, pp. 697-703.
8. Bernstein, A.: *Medicine*, 19:85, 1940.
9. Bassen, Frank A., Thompson, Annis E. and Silver, Aaron: *J. Lab. Clin. Med.*, 34:543-548, 1949.
10. Davidsohn, I.: *J. Immunol.*, 16:259-273 (March) 1929.
11. Davidsohn, I., Stern K. and Kashiwagi, C.: *Am. J. Clin. Path.*, 21:1101-1113 (Dec.) 1951.
12. Davidsohn, I. and Walker, P. H.: *Am. J. Clin. Path.*, 5:455-465 (Nov.) 1935.
13. Custer, R. Philip and Smith, Edward D.: *The Pathology of Infectious Mononucleosis*. George R. Minot Symposium on Hematology. Edited by Dameshek and Taylor. Grune and Stratton, 1949, pp. 704-731.

SOME RECENT CONCEPTS IN CARCINOGENESIS

A. C. RITCHIE, M.D.* and PHILIPPE SHUBIK, M.D.**

The number of agents able to induce tumors in man or animals is now known to be very large. Even if all the physical carcinogens, such as x-rays and ultraviolet light, and all the mixtures of impure substances, such as tars and oils, are omitted, and only pure chemical substances considered, the number is still considerable. Hartwell¹ reviewed the literature and found that by the end of 1947 no less than 357 pure substances had been reported carcinogenic. These "pure carcinogens" are of many different chemical families, as widely separated from one another as diepoxides², the derivatives of benzantracene, the salts of beryllium, and the azo-dyes; and their biological behavior is no more uniform. Some are effective if given by mouth, but ineffective if painted on the skin; others ineffective when given by mouth, but effective when painted on the skin. Butter yellow given by mouth to rats produces tumors of the liver and only of the liver; 2-acetylaminofluorene given in the same way produces tumors of a great many epithelial organs, the liver among them³. If beryllium is injected intravenously in rabbits, sarcomata of bone are induced⁴, but 1,2,5,6-dibenzanthracene⁵ given intravenously to mice induces lung tumors. In short, the carcinogens differ so greatly one from another, both chemically and biologically, that it is impossible to draw any general conclusions from the study of any one of them, or any one series of them. The same may be said of secondary factors influencing carcinogenesis. Because the concentration of riboflavin in the liver has been found of importance in carcinogenesis by the azo-dyes⁶, there is no reason to assume that it will be of importance in carcinogenesis by 2-acetylaminofluorene. Croton oil can sometimes augment the carcinogenic activity of certain of the derivatives of benzantracene⁷, but there is no reason

to think that it could affect carcinogenesis by one of the stilbenes. The greatest caution must, therefore, be exercised before any general conclusion is drawn from a single group of experiments and applied to carcinogenesis as a whole.

Perhaps the most studied of all carcinogens have been those of the benzantracene series, a group of compounds very similar both chemically and biologically. In this group fall such well-known substances as 1,2,5,6-dibenzanthracene, 3,4-benzpyrene, 20-methylcholanthrene, and 9,10-dimethyl-1,2-benzanthracene. Only a few tissues and a few animals are susceptible to the carcinogenic action of the compounds of this group. Tumors are easily induced in the skin of the mouse or the rabbit and in the fibrous tissue of the rat or the mouse; but in other tissues and animals the results are variable and dependent on many factors not yet understood. In order to produce tumors these carcinogens must be brought into intimate contact with susceptible tissue. They must be painted onto the skin or injected into fibrous tissue. In every case a considerable interval elapses between the start of the treatment with the carcinogen and the appearance of a tumor.

The changes occurring in tissues so treated have been studied histologically. When a carcinogen of this series is applied to the skin of a mouse or a rabbit, the skin rapidly becomes hyperplastic. Some weeks later, small, benign tumors appear in this hyperplastic skin. Some of these papillomata will grow slowly throughout the lifetime of the animal; others become stationary; others regress; and yet others become malignant⁸. The differences between the various types of papillomata do not seem to be permanent. A papilloma which has become stationary may begin to grow again, or may regress; a tumor which has regressed may recur. Only when the tumor has become malignant does the change seem irreversible. The formation of the fibrous tumors has also been studied. Un-

*Visiting faculty member from Oxford University, in Laboratory of Cancer Research.

**Assistant Professor of Surgery, Coordinator of Oncology, The Chicago Medical School.

fortunately, it is very difficult to distinguish between fibrous hyperplasia, benign fibroma, and fibrosarcoma. It does seem that there may be a succession of changes similar to those seen in the skin, that there may be hyperplasia, then benign neoplasia, and then malignant transformation, but the evidence is not nearly so clear.

The metabolism of these carcinogens has been studied in some detail, but as yet little of importance has been discovered. A number of metabolites have been isolated, but they are all of types that would be expected, and do not differ from those produced when similar but non-carcinogenic compounds are detoxified. There is nothing to suggest how the carcinogen modifies the affected cells. Rather more success has been achieved in the localization of carcinogen within the cell. Ultra-violet microscopy⁹ has shown that there is a concentration of carcinogen about the nuclei, perhaps in the mitochondria. It cannot, of course, be deduced that the carcinogen acts by modifying the mitochondria. Another interesting report is that in the case of benzpyrene, at least part of the carcinogen, or one of its metabolites, is conjugated with protein¹⁰. Once again it is not permissible to make any general deduction. However, these findings do give hope that some more important discoveries may be made as this biochemical work is pursued.

What is perhaps the most interesting of the recent advances was made in quite another way. From the early days of chemical carcinogenesis it was apparent that the action of carcinogens could be modified in various ways. In particular, it was found that a noncarcinogenic substance, croton oil, added to a weak solution of benzpyrene greatly augmented its power to induce tumors in mouse skin. In one experiment, when a weak solution of benzpyrene was applied repeatedly, only 3% of the mice got tumors; when croton oil was added to the solution of carcinogen, 26% got tumors⁷. Croton oil has been called a "co-carcinogen"; that is, a substance which can augment the power of some carcinogens, but which is itself non-carcinogenic. The next

step was the discovery that a single application of carcinogen was able to prepare mouse skin so that subsequent repeated applications of croton oil could make tumors manifest in the prepared skin¹¹. Even a dose of carcinogen so small that of itself could produce no tumors at all was found sufficient to prepare the skin so that croton oil could make many tumors manifest. Applied before the carcinogen, croton oil was without effect¹². Only when applied to skin that had been treated previously with carcinogen could it affect carcinogenesis.

The explanation of these phenomena seems simple. The carcinogen prepares the skin, modifying some cells or groups of cells in such a way that croton oil becomes able to make them manifest as tumors. The importance of this finding is that carcinogenesis has been divided into two steps or stages. In the first stage, cells are prepared by carcinogen, so that in the second, the noncarcinogenic croton oil can make tumors manifest.

A good deal is known about these two stages. When tumors are produced in the skin of the mouse by a single application of a carcinogen of the benzanthracene series followed by repeated applications of croton oil, there comes a time after which few or no tumors appear. For example, in Swiss strain mice, tumors begin to appear about the fifth week after the first application of croton oil and new tumors continue to appear until about the twentieth week, but after that time few, if any, new tumors are produced. From this it can be deduced that the carcinogen does not change all the cells in the skin in such a way that croton oil is able to make them manifest as tumors. If it did, one would expect to see not the few tumors that are found on each mouse, but one massive tumor, in which the whole of the prepared skin was manifest as tumor. Such a general tumorization is never seen.

The change produced by the carcinogen is known to be relatively sudden. It can be produced by a single application of carcinogen, and is presumably complete by the time that the carcinogen has disappeared from the skin. Opinion differs as to how long the carcinogen does

remain after a single application, but the time is probably not longer than a few days⁹. Thus, the preparation of the skin must also be complete in a few days. Again, the change produced by the carcinogen is permanent. The same number of tumors are produced whether the interval between the application of carcinogen and the first application of croton oil is as short as 3 days or as long as 43 weeks¹³. It has also been demonstrated that the total number of tumors induced is related semilogarithmically to the concentration of carcinogen used in the single initial application. Further studies along these lines are in progress at The Chicago Medical School, and it is possible that more knowledge of the biological mechanisms involved may be obtained.

The process by which croton oil makes these prepared cells manifest as tumors is very different. It is not sudden, for many applications of oil must be given before any tumors appear. It is not permanent, for some of the papillomata produced regress. It seems to determine the time it takes to make tumors appear, for tumors appear the same time after the first application of croton oil whatever the carcinogen used, and whatever its concentration. For example, in the Swiss strain mouse, tumors appear on the average ten weeks after the first application of croton oil. This time is not affected by changing the carcinogen used to prepare the skin or by altering the interval between the application of carcinogen and the beginning of the use of the croton oil. There have been some who thought, and perhaps some who still think¹⁴, that croton oil acts by causing a general hyperplasia of the skin, and that any general growth stimulus would serve to make the changed cells manifest as tumors. This is not so. A great many very potent growth stimulators have been tested, substances which cause a marked hyperplasia of mouse skin, but no other noncarcinogenic compound has been able to manifest tumors in prepared skin¹⁵. The action of croton oil does not depend on any nonspecific quality, but is due to some specific power, the nature of which is quite unknown.

It was said that great caution must be

exercised before any general conclusions are drawn. So far only the action of the carcinogens of the benzantracene series has been considered; and in only one particular instance, carcinogenesis in mouse skin, has their carcinogenic action been divided into stages. This evidence is far too slight to permit generalization. However, if the possibility that carcinogenesis might consist of a number of stages is examined in other instances, more evidence can be obtained.

Compounds of the benzantracene series are also able to prepare the skin of the rabbit so that a subsequent noncarcinogenic stimulus is able to make tumors manifest. In this case croton oil is ineffective, and the only competent noncarcinogenic stimulus known is deep trauma¹⁶. No satisfactory demonstration of stages in subcutaneous carcinogenesis has been made, and it is hard to design such an experiment. It has been found, though, that croton oil acts as a co-carcinogen, augmenting the carcinogenic power of the compounds of the benzantracene series when they are applied to fibrous tissue, just as it does when they are applied to mouse skin¹⁷.

Turning now to other types of carcinogens, it can be said at once that in no case has carcinogenesis been clearly divided into stages. Nevertheless, there is some very suggestive evidence. In the rat, a dose of 2-acetylaminofluorene far too small to produce any tumors has been shown able to prepare the thyroid so that subsequent administration of thiouracil can make tumors manifest in that gland¹⁸. The importance of this finding is lessened by the fact that thiouracil alone is able to produce tumors of the thyroid in rats, though it takes much longer to act than when acetylaminofluorene is given first. In other cases, noncarcinogenic substances have been shown to have co-carcinogenic power. For example, in rats, progesterone given at the same time as acetylaminofluorene greatly increases the number of breast tumors which appear. Alone, it is without carcinogenic power. Such evidence suggests that it might be possible to demonstrate a division into stages by giving a subliminal dose of acetylaminofluorene and following it by

progesterone, but the demonstration is yet to be made.

The best evidence that other kinds of carcinogenesis may be a staged process comes from some publications by Foulds.^{19,20,21} He studied the natural history of various kinds of tumors, papillomata, and carcinomata of the bladder induced by acetylaminofluorene in rats, spontaneously occurring fibroadenomata of the breast in rats, and more particularly, spontaneously occurring mammary tumors of mice. He found that, in each case, the tumors fell into a few groups, each with a specific growth pattern. Some of the mouse breast tumors, for example, grew at a steady rate which was uninfluenced by pregnancies; others grew rapidly during pregnancy, to regress afterwards. He found that from time to time a tumor would change its habit of growth, perhaps changing from the type which regressed at the end of each pregnancy to one which grew steadily and was uninfluenced by pregnancy. These changes might be gradual or sudden, but were permanent. There seemed to be several states in which a mouse mammary tumor could exist, and individual tumors made step-like changes from one to another of these states. Here,

tumor growth, like carcinogenesis, seems to be a staged process.

Looking back at the work with the carcinogens of the benzanthracene series, it seems that there might be another example of the type of change that Foulds described. Applied repeatedly to the skin of mice these carcinogens produce papillomata, some of which become malignant. Might not the change from papilloma to carcinoma be another step in a chain of reactions which together make carcinogenesis and tumor growth?

In summary, it can be said that in a few cases carcinogenesis and tumor growth have been shown to be staged processes. Further experiments with other types of carcinogens, in other tissues and other animals, are needed before generalizations can be made. In particular, more attention should be paid to human tumors. In man it would not be proper to try to induce experimental tumors with carcinogens and croton oil, but it is possible to record the natural history of the spontaneously occurring neoplasms. Such studies might make it possible to demonstrate that in man, as in animals, carcinogenesis and tumor growth are staged processes.

REFERENCES

1. Hartwell, J. L., Survey of compounds which have been tested for carcinogenic activity. Federal Security Agency, U. S. Public Health Service, 1950.
2. Fovland, E. A review. *Cancer Research*, 12:77-84, 1952.
3. Wilson, R. H., DeEds, F., and Cox, A. J., *Cancer Research*, 1:595-608, 1941.
4. Dutra, F. R., and Largent, E. J., *American Journal of Pathology*, 26:197-209, 1950.
5. Andervont, H. B., Public Health Report, U. S. Treasury Department, 52:637-646, 1937.
6. Miller, E. C., Miller, J. A., Kline, B. E., Rusch, H. P., *The Journal of Experimental Medicine*, 88:89-98, 1948.
7. Berenblum, L., *Cancer Research*, 1:44-47, 1941.
8. Shubik, P., *Cancer Research*, 10:713-717, 1950.
9. Ahlstrom, C. G., and Berg, N. O., *Acta Pathologica et Microbiologica Scandinavica*, 26: 496-506, 1949.
10. Miller, E. C., *Cancer Research*, 11:100-108, 1951.
11. Mottram, J. C., *The Journal of Pathology and Bacteriology*, 56:181-187, 1944.
12. Berenblum, L., and Shubik, P., *The British Journal of Cancer*, 1:379-382, 1947.
13. Berenblum, L., and Shubik, P., *The British Journal of Cancer*, 3:384-386, 1949.
14. Billingham, R. E., Orr, J. W., and Woodhouse, D. L., *The British Journal of Cancer*, 5:417-432, 1951.
15. Shubik, P., *Cancer Research*, 10:13-17, 1950.
16. Friedewald, W. F., and Rous, P., *The Journal of Experimental Medicine*, 80:101-126, 1944.
17. Klein, Michael, *Journal of the National Cancer Institute*, 11:843-848, 1951.
18. Hall, W. H., and Bielschowsky, F., *The British Journal of Cancer*, 3:534-541, 1949.
19. Foulds, L., *Annals of the Royal College of Surgeons of England*, 9:93-101, 1951.
20. Foulds, L., *Journal of the Royal Microscopical Society*, 70:173-180, 1950.
21. Foulds, L., *The British Journal of Cancer*, 3: 345-375, 1949.

ACUTE PANCREATITIS*

MARTIN M. KIRSHEN, M.D., F.A.C.P.**

Years ago, the diagnosis of acute pancreatitis was usually made on the operating table on patients in whom the preoperative diagnosis was either cholelithiasis, perforated ulcer, or intestinal obstruction. Pancreatitis was considered to be a rare condition.

Since we have become more pancreatitis conscious, we have learned that this clinical entity is not as rare as it was formerly believed to be and that it may be diagnosed if the possibility of its presence is considered.

It is common knowledge that acute pancreatitis is more frequent in the male, that it occurs mostly between the ages of forty and sixty, that cholelithiasis and cholecystitis are often primary or associated lesions, that obesity is common in patients with pancreatitis, and that in many instances there is a history of alcoholism or at least that the attacks of the disease occur after heavy meals or drinking bouts.

The pathology of acute pancreatitis as expressed in tissue changes is well known and described. It is unique in its particular features because it is neither a simple inflammation or an infectious process nor a purely hemorrhagic or necrotizing lesion; it may present several or all of these features at the same time.

As a result of observations at necropsy and at operations, together with studies of the laboratory findings in this disease, it has been established that acute pancreatitis is not always associated with recognizable hemorrhage and necrosis, as it was formerly believed to be. There are fortunately many instances of a less severe course of the disease, with a short duration and complete recovery.

Therefore, two forms of acute pancreatitis are described: (1) The acute interstitial; and (2) the acute hemorrhagic or necrotizing pancreatitis. The first form

is mild and transient, characterized by a glossy edema of the gland and similar changes in the peripancreatic tissue, mesocolon, and root of the mesentery. Only few and small foci of necrosis are seen and there is a relatively small amount of a clear or brownish colored fluid in the peritoneal cavity and in the small omentum. The fluid is rich in activated enzymes. This form most commonly occurs in association with acute or chronic episodes of diseases of the biliary tract.

In the second, severe or hemorrhagic form, the enlarged pancreas shows extensive areas of necrosis and the gland may occasionally be converted into a mushy, friable, dark brown mass. Because of the high tryptic activity of the fluid present in the abdominal cavity, hemorrhages are extensive. When the lipolytic activity predominates, whitish areas of fat necrosis are widely scattered throughout the abdomen. Due to hydrolysis of fat, fatty acids are present in these areas and may attract large amounts of calcium, producing a newly recognized symptom of acute pancreatitis — hypocalcemia.

What is the etiology and what are the basic mechanisms underlying these various types of lesions?

Infection was considered an important factor because it was known that parotitis, typhoid fever, and scarlet fever may be associated with pathologic changes in the pancreas. But these changes are of mild character and have a tendency to disappear during recovery from the main disease. Abdominal trauma and vascular accidents like embolism or thrombosis may in some cases be the cause of pancreatitis but it is an experimentally established fact that lesions of the type found in acute pancreatitis can only be produced by the action of the activated enzymes of the pancreatic juice on the gland itself.

The pancreas empties its secretion into the duodenum through the main pancreatic duct. Here, in the duodenum, the enzymes of this secretion become active.

* Presented at the alumni meeting of The Chicago Medical School in 1952.

** Associate professor of medicine, The Chicago Medical School; senior attending, Michael Reese Hospital; attending, Mount Sinai Hospital.

vated by different constituents of the bile and participate prominently in the digestion of fat, carbohydrates, and protein. As the pancreas, in the manner of any other secretory gland, empties its contents with a definite secretory pressure, the question arises of how these activated enzymes or the biliary constituents capable of such activation find their way into the gland against this pressure.

Among several propounded theories, the theory of the so-called "common channel" has the best physiological, experimental, and clinical foundation and evidence.

The openings of the main pancreatic duct and the common bile duct have a peculiar anatomical relationship which, in the majority of cases, may explain a pre-existing common channel. Although the two duct openings may occasionally be separate, they enter the duodenum in the majority of cases through one orifice which is surrounded by the Sphincter of Oddi. A further important anatomical feature of these two ducts is the length of the septum between them. When the septum is long enough, closure of the common sphincter will not lead to a mixture of the pancreatic juice with the bile before the ducts empty their contents into the duodenum. But when the septum is short enough to permit the formation of a common channel, a stone at the papilla or a reflexly produced and prolonged spasm of the sphincter (often due to some biliary tract pathology) will give ample opportunity for the pancreatic juice to mix with the activating bile constituents. Gall bladder contractions or increased secretory pressure of the liver will drive activated enzymes back into the pancreas. The stage for the development of acute pancreatitis is set. Activated pancreatic juice accumulates under pressure in the pancreas and diffuses into the peri-pancreatic tissue and edema of the pancreas develops. As this fluid is absorbed into the circulation, pancreatic enzymes in increased amounts, (hyperenzymia) are found in the blood.

Why is there edema in some cases and hemorrhages and necrosis in others? As the mechanism is the same in both types of the disease, why the difference? The

best concept concerning the pathogenesis of acute pancreatitis at the present time is that its different pathological features are manifestations of the same basic process and that the presence or absence of some of these features are largely determined by additional factors, some of which are known and others are unknown. These factors, for example, may be: coincidental richness of the pancreatic juice in enzymes due to a stimulating heavy meal or alcohol; coincidental vasospasm or excessive vasodilation with consequent anemic or stagnant anoxia increasing the vulnerability of the pancreas; shock in an overwhelming attack of cholelithiasis may advance a pancreatic edema to an acute necrosis. I can even imagine a case of cholelithiasis treated with excessive doses of morphine and followed, because of this, by an acute pancreatitis. It is often forgotten that opium and its derivatives are cholinergic drugs and may produce long lasting spasm of the Sphincter of Oddi.

Acute pancreatitis may mimic not only abdominal but also thoracic emergencies. The beginning is often dramatic in its suddenness, usually occurring a few hours after a heavy meal or after an excessive intake of alcohol. In about 50% of cases, a history of cholecystitis or cholelithiasis can be elicited and a tentative diagnosis of these conditions is made. There is an agonizing, persisting pain in the epigastrium, radiating to the left and to the back, but not infrequently also to the right. The pain in pancreatitis, characteristically, responds poorly to the usual doses of narcotics and may be so severe as to produce a shock-like condition. There is diffuse tenderness of the abdomen and rigidity in the epigastric region, although not as outspoken as in a perforated ulcer. The distention, silent abdomen and constipation present may duplicate the picture of a paralytic ileus. The shock, the occasional radiation of the pain into the chest, nausea, and vomiting may suggest coronary occlusion. To add to the confusion, not uncommonly, changes indicative of myocardial damage are found in the EKG. These changes are believed to be the result of shock, particularly in older individuals with arteriosclerotic hearts. An additional contribu-

tory factor is the often decreased serum potassium, due to vomiting, treatment with fluids, or Wangensteen suction. Pleural effusion in the left chest is of common occurrence and areas of ecchymosis may be present around the umbilicus and along the flanks (so-called Gray-Turner sign).

The diagnosis is difficult and sometimes impossible without important laboratory information. We can get this information only when we are pancreatitis conscious in our work-up of abdominal emergencies. Ordering blood chemistries, counts, urine examinations, x-ray, etc., we must not forget to ask for amylase and lipase determinations of the serum, and we must ask for them, if possible, as soon as we see these patients or as soon as they arrive in the hospital. Speedy amylase determination is important because of the fact that the serum elevation of this enzyme in acute pancreatitis lasts only a short time (24-36 hours) and because it takes only about one hour for the test to be performed in the laboratory. The increase in lipase lasts longer, but is slower in development and it takes 24 hours before the test is completed.

Lately, some important observations were made regarding the elevation of these enzymes in some other conditions. It was found that they may occur in perforating ulcers, peritonitis, intestinal obstruction, and after the use of opium and its derivatives. The values of the enzymes in the mentioned conditions, although never as high as in acute pancreatitis, have to be carefully evaluated. Values above 500 mg. speak definitely for pancreatitis. (Normal values for amylase with the Somogyi method are 125 mg. glucose; normal value for lipase 1.5 cc. of a 1/20 normal hydroxide).

In the current year, a new and very promising test was introduced — the anti-thrombin determination of the serum. It seems that in acute pancreatitis, the anti-thrombin titer and the prothrombin time are markedly increased, giving a good explanation for the hemorrhages in the abdominal cavity and for the Gray-Turner sign.

Acidosis, but sometimes hypochloremia and alkalosis, hyperglycemia, glycosuria,

and hypocalcemia are further important and supporting laboratory findings in the more severe cases. The development of a so-called lower nephron syndrome with azotemia is not uncommon in the cases with a shock-like condition.

Of interest is the differential white count. Leukocytosis is always present in acute pancreatic edema, but associated lymphopenia indicates pancreatic necrosis and is of significance in evaluating the course and severity of the condition.

The greater the lymphopenia at the onset, the more extensive is the necrosis and the poorer the prognosis. Lymphopenia quickly replaced by lymphocytosis is a good omen.

It is agreed by all authorities that the treatment of acute pancreatitis should be medical and conservative. The treatment should take into account the pathogenesis of the disease and should be based on and directed by physiologic considerations.

As it is known that the changes in the pancreas and the tissue around the pancreas are due to a "deviation" of the pancreatic enzymes from their normal pathways, every attempt should be made to relieve the possible spasm of the Sphincter of Oddi, to stop or diminish pancreatic secretion, and to avoid carefully every known physiologic and pharmacologic stimulation of the gland.

The external secretion of the pancreas is normally controlled by the stimulation of the vagi and by hormone secretion, for which the trigger mechanism is the entrance of the acid ingesta into the duodenum. Therefore, vagotonic drugs like prostigmine, urocholine, and morphine and its derivatives should be avoided. They not only stimulate the pancreatic secretions but in addition increase the tonus of the Sphincter of Oddi. If the use of any of these drugs is unavoidable, large doses of atropine should be given simultaneously. Even Demerol, which was considered the drug of choice, was found by Pickering to have the same vagotonic effects as morphine.

What then should be used for the excruciating pain in acute pancreatitis? Incredible as it sounds, when the patient is not in shock and the pain not to ex-

treme, amyl-nitrite or nitroglycerine may bring relief. In overwhelming pain, 300-500 mg. of tetraethylammonium chloride, intravenously, repeated every four to six hours, may give excellent results. Popper recommends uni-or bilateral paravertebral procaine block and I have seen very gratifying results from this procedure. It is interesting to note that, in experimental animals in which the pancreatic ducts and the supplying blood vessels have been ligated, tetraethylammonium chloride prevents the necrosis of the pancreas which develops in a control group of animals which does not receive the drug.

To prevent hydrochloric acid from entering the duodenum and provoking stimulation and increased pancreatic secretion, a Levine tube should be inserted and the gastric contents removed by constant suction. No food should be given by mouth until the patient improves.

Ephedrine in doses of 2.5 mg., atropine in doses of 0.4 mg., or Banthine (which lately proved to be the drug of choice) in doses of 100 mg. subcutaneously every six hours may be of considerable help in checking pancreatic secretions.

The administration of intravenous fluids has to be regulated by frequent determination of the electrolytes, (potassium should not be forgotten). The best fluids are saline solution, plasma, and blood. Glucose solution should be used as sparingly as possible and then only

in 2½% concentration—at least for the first few days. It is a known fact that hyperglycemia stimulates pancreatic secretion and as hyperglycemia is frequently encountered in acute pancreatitis, additional sugar solution would defeat the purpose of our treatment.

Although insulin may be used to reduce the hyperglycemia, it has to be given with caution and in small doses in order not to produce hypoglycemia, which is an even more potent stimulus of pancreatic secretion than is hyperglycemia.

Amino-acids intravenously produce profuse pancreatic secretion and should be avoided. Antibiotics, like penicillin or aureomycin, given intravenously, are of benefit in preventing peritonitis and other complications. With improvement, the patient should be placed on a bland diet with small and frequent feedings, as in ulcer treatment. With a careful and closely supervised management, based on physiologic considerations, even severe cases may recover.

Surgical attempts to drain the biliary channels are seldom made today and I would hesitate to recommend any of these procedures. If a known pathological condition of the gall bladder and the biliary tract exists, surgery after complete recovery may be indicated in order to prevent recurrences of the condition. Occasionally, abscesses of the abdominal cavity may have to be drained.

CLINICOPATHOLOGIC CONFERENCE

Presented at the Mount Sinai Hospital, Chicago

DR. L. FELDMAN, Chairman

DR. I. DAVIDSOHN, Secretary

Abstracted by DR. A. OYAMADA

1st Admission: This 51-year-old white male was admitted to Mount Sinai Hospital on February 23, 1949, for operative repair of a right inguinal hernia which had been present for four years. Surgery had been refused by his physician 2½ years previously because of an enlarged spleen and an elevated red count. Since that time, several venesections, totalling 8 pints of blood, and several courses of radioactive phosphorus were undertaken at the Mayo Clinic and at the Cook County Hospital. Six months before admission, he had severe epistaxis which required cautery to stop the bleeding. He lost ten pounds in weight during this six month period.

On examination, his state of nutrition was satisfactory; temperature was 98.8° F., pulse 84, respiration 20, and blood pressure 190/105. The skin was dusky. A reducible, orange-sized mass was found in the right scrotal sac; the external inguinal ring easily admitted two fingers. The spleen was enlarged to 12 cm. below the left costal margin. The liver and kidneys were not palpable. The chest was clear. Cardiac findings were negative except for accentuation of the aortic second sound consistent with the elevated blood pressure. Pedal edema was absent. The admission red blood count was 5.50 million, hemoglobin 10.8 gm. (69.2%), and color index 0.62.

A hernioplasty was carried out on February 25, 1949. On the next day the right testis became enlarged, tender, and edematous. The swelling gradually subsided and the patient was discharged improved on March 26, 1949.

2nd Admission: The patient returned to this hospital on May 27, 1950. In the interim, he had been followed in the medical and urology outpatient clinics for generalized weakness, headaches, anorexia, nocturia, polyuria, and occasional dysuria. Six weeks before this admission an episode of chills and fever

(104°F.) was treated by his physician with penicillin and sulfa. An intravenous pyelogram was entirely negative. On May 20, 1950, his red blood count was 7.06 million, hemoglobin 13.5 gm. (77.4%), color index 0.62, and white blood count 37,500. There was a weight loss of eleven pounds.

The cause for this admission was acute dyspnea and cyanosis, developing within two hours, with a drop in blood pressure to 85/56, rapid irregular respirations, and a feeble rapid pulse (130/min). Some relief was obtained by immediate administration of intravenous morphine (gr. ¼), atropine (gr. 1/150), aminophylline (gr. 7½), crystidigin (0.4 mg.), and positive pressure oxygen. The blood pressure rose to 126/76.

Pertinent physical findings: marked cyanosis of the face and lips; venous distention of hands, forearms, and neck; emphysematous chest with impaired resonance and coarse rales in the right posterior base; moderate left heart enlargement, rate 130, regular rhythm with occasional extrasystoles; liver edge down 10 cm.; splenic edge down, 13 cm. and firm; two-plus edema of both ankles.

On the second hospital day, sudden pain appeared in the left flank. Catheterization, carried out to determine the basis of this pain, was followed by swelling of the right testis and cord and by a temperature rise to 101.4°F. The swelling gradually diminished with the administration of local wet packs and penicillin. After a sternal marrow aspiration, which showed hyperplasia and active erythropoiesis compatible with polycythemia, the patient was discharged on June 11, 1950.

3rd Admission: The patient's next admission to this hospital was on August 15, 1950, for dyspnea, generalized weakness, and progressive ankle edema of six weeks' duration. His appetite continued to be poor. He had received digitalis and

mercurials through the outpatient clinic. For three months he had had chilly sensations and fever (102°F.) in the evenings.

After admission, the temperature never was found above 99.6°F. His blood pressure was 178/80. Adenopathy was absent. The chest was clear. In view of a hemoglobin of 9.5 gm., and a white blood count of 40,600 with immature granulocytic cells, hematology consultation was requested. The consultant confirmed the physical and hematologic findings and also pointed to the numerous basophiles, occasional nucleated red blood cells, normal platelets, albuminuria, pyuria, and punch tenderness over the right kidney area. Several factors were felt responsible for the patient's condition: iron deficiency from poor iron intake (low meat diet) and venesections or from gastrointestinal bleeding plus the above two factors; a genitourinary tract infection; polycythemia vera with possible leukemic change; vitamin B deficiency. Iron therapy, urine culture, and intravenous pyelograms were suggested.

An iliac crest marrow aspiration revealed findings compatible with severe gastro-intestinal tract bleeding as may be found in polycythemia. The stomach x-rays were negative. There was poor excretion and poor visualization of the renal pelves on intravenous pyelography. A few hemolytic and non-hemolytic *Staphylococcus aureus* were isolated on urine culture. A later blood count showed: red blood count 6.15 million, hemoglobin 10.1 gm. (65%), color index 0.53, white blood count 53,500, 3 myelocytes, 1 metamyelocyte, 3 stab cells, 2 eosinophiles, 16 basophiles, 1 lymphocyte, and 3 monocytes. The patient was discharged on September 7, 1950.

4th Admission: The patient was readmitted to Mount Sinai Hospital on October 13, 1950, because of severe pain in the right side of the abdomen with nausea and vomiting for three days. The vomitus contained coffee-ground material. On the day after admission there was extreme swelling and pain in the right shoulder. On examination this was found to be due to a large hematoma in

the chest wall. The right chest presented dullness to percussion and diminished breath sounds. There was pitting dependent edema. The sclerae were mildly icteric. The left heart border was 15 cm. from the midsternal line. Systolic mitral and aortic murmurs were audible. The red count had dropped to 2.99 million; hemoglobin was 5.8 gm. (37.1%); the color index was 0.62; the white blood count was 59,200, and platelets 552,000.

The chest wall hematoma was periodically aspirated with a large needle, yielding as much as 150 c.c. of thick blood on two occasions. Serial chest x-rays demonstrated peribronchial infiltration and increased density in the right cardiophrenic angle. The patient remained afebrile. He was discharged to the hematology outpatient clinic on November 3, 1950.

5th Admission: The patient was hospitalized here again nine weeks later, on January 1, 1951, with increasing weakness and frequent paroxysmal nocturnal dyspnea. At this time both lower lung fields showed dullness to flatness, diminished breath sounds, and rales. His blood pressure was 196/104. Cyanosis was absent. The heart tones were distant, although the aortic second sound was accentuated. Dependent edema and hepatosplenomegaly were still present.

Therapeutic measures included aminophylline, mercurhydrin, low salt diet, and barbiturates. Later, a course of digitalis was given. On the third hospital day, he had an attack of paroxysmal nocturnal dyspnea with chest pain and a temperature of 103.8°F., relieved by intravenous aminophylline. Except for this incident, the subsequent clinical course was marked by steady improvement and he was discharged to a convalescent home on February 8, 1951.

6th Admission: The patient's sixth admission to this hospital was on April 29, 1951, for colicky right costovertebral angle pain, present for two days, radiating into the right groin and genitalia. This was accompanied by burning on urination. There was a positive Murphy sign in the right renal area. The urine had many granular casts and two plus albumin, but no pus cells. The specimen

on the next day had no casts. The white blood count was 146,100 with a shift to the left of the granulocytic series. There were no nucleated red cells.

A urologic workup was undertaken. An intravenous pyelogram showed a left-sided hydronephrosis but no evidence of a calculus. Cystoscopy revealed a moderately enlarged prostate, a trabeculated bladder, a non-visualized right ureteral orifice, and a normal left ureteral orifice. The bladder mucosa was studded with many soft small calculi, found chemically to be mainly oxalates. Following the above procedures, the patient was discharged on May 9, 1951.

7th (Final) Admission: The patient returned to this hospital on May 28, 1951. Five hours previously, while sitting in a chair, he had had a sudden attack of shortness of breath with wheezing. His lower extremities had become more swollen in the last two days.

Examination revealed generalized pallor and evidence of weight loss (30 lbs. in the past year). The fingers were slightly clubbed. All lung fields were filled with moist coarse rales; breath sounds were diminished. The neck veins were greatly distended. Percussion revealed marked left heart enlargement. His blood pressure was 180/100; pulse 96 and regular. The liver edge was 10 cm. below the costal margin and the splenic edge at the level of the left iliac crest. Ascites and four plus dependent edema were noted.

With immediate oxygen therapy, mercuhydrin, aminophylline, and later digitalis, the lungs cleared. On June 7, 1951, severe bleeding per rectum was encountered. This was thought to originate from an indurated mass 2 cm. in diameter located 4 cm. from the anus. Two separate biopsies were obtained from the mass at proctoscopy and the bleeding was stopped by packing. A barium enema x-ray was non-contributory.

On July 8, 1951, while the patient was at stool, the scrotum suddenly became distended and painful. At surgery, the right testis was found to be swollen and engorged. Postoperative wound healing was difficult due to local bleeding. Frequent blood transfusions were required

because of low hemoglobin levels (av. 5.6 gm. or 35.9%). On the evening of July 20, 1951, there was profuse hemorrhage from large arterial bleeders in the operative wound with preshock, requiring the tying of these vessels and pressure dressings.

Hematology consultation was obtained on July 23, 1951. Pronounced bleeding trends in the past three weeks despite the high platelet count and normal clotting time suggested either myeloid metaplasia or leukemia. During the next week there was a return of dyspnea, moist rales in the lungs, asthmatic breathing, and 3 plus pretibial edema. But an excellent response was obtained with aminophylline, mercuhydrin and oxygen therapy. In the next few days, there was some distress in the epigastrium and lower sternum following meals which could not be correlated with any definite pulmonary or cardiac findings. Otherwise, the patient appeared to be doing well. However, after midnight on August 13, 1951, the patient became acutely dyspneic, weak, and restless. The pulse became weak, blood pressure dropped to 66/30, and respirations dropped to 8 per minute. He failed to rally with various stimulants and died five hours later.

Dr. J. Arendt, Roentgenologist: The patient received radioactive phosphorus—in fact, several courses of it—at the Mayo Clinic and Cook County Hospital. In view of later developments, one would like to have a more definite statement about the dosage and the form of application. The average dosage is approximately 4-6 millicuries. Overdosage might lead to hematopoietic depression and might effect a change from polycythemia to leukemia or aplastic anemia.

He also had a considerable amount of external radiation. He was repeatedly examined in several places for gastrointestinal, kidney, and chest pathology. It might, therefore, be legitimate to ask whether radiation of one kind or another has not contributed in this case to the transition from a clear polycythemia to a myelogenous hyperplasia or myeloid leukemia.

As a diagnostic problem, the patient

LABORATORY DATA

Blood Count:	RBC	Hb.	C.I.	WBC	Myel.	Meta.	Stabs	Segs.	Eos.	Pas.	Lyms.	Mono.
First Admission												
2/23/49	5.50 Mill.	10.8gm. 69.2%	0.62	8,350	0	0	0	74	3	3	15	5
Outpatient												
5/20/50	7.06	13.5gm. 87.4%	0.62	37,500	6	0	3	70	5	6	8	2
Second Admission												
5/27/50	6.48	12.8gm. 82%	0.64	48,000	0 (1 blast)	1	7	74	2	8	5	3
Outpatient												
6/23/50	3.41	8.5gm. 55%	0.81	33,600	0	5	4	72	7	9	12	2
Third Admission												
8/16/50	4.00	9.1gm. 58.3%	0.72	40,600	0	0	6	76	1	9	3	5
9/5/50	6.15	10.1gm. 65%	0.53	53,500	3	1	3	71	2	16	1	3
Fourth Admission												
10/14/50	2.99	5.8gm. 37.1%	0.62	59,200	0	2	1	89	0	4	2	3
Fifth Admission												
1/24/51	6.10	10.1gm. 64.7%	0.53	45,900	2	1	12	63	2	10	8	2
Sixth Admission												
4/30/51	5.27	10.0gm. 64.1%	0.62	146,100	3 (1 blast)	4	21	51	3	12	3	2
Seventh Admission												
5/28/51	5.70	10.3gm. 66%	0.63	54,300	3	2	19	56	1	4	11	4
7/21/51	2.05	4.6gm. 29.5%	0.61	44,600	1	2	11	77	0	4	4	1
7/31/51	4.65	14.4gm. 92.3%	1.01	40,500	0	0	3	86	1	1	9	0

Anisocytosis, poikilocytosis, hypochromia, polychromatophilia, and targetting were present almost constantly.

Toxic white blood cells, nucleated red corpuscles, and hypersegmented neutrophils were present on many counts.

The platelet count ranged from 240,000 on 5/31/50 to 1,214,000 on 7/13/51, but there was no regular progression.

The prothrombin time ranged from 15 sec. to 40 sec. (clotting activity 73% to 40% of normal). This followed no definite progression.

was sent to us first for the exclusion of a malignancy. The stomach shows no evidence of deformity, other than pressure by an enlarged spleen. The spleen is greatly enlarged and presses on the colon as well as on the stomach. The stomach is displaced far to the right side. No ulceration is seen, but the folds in the lower esophagus and fundus region show some exaggeration and widening. They are not sufficiently tortuous and wormlike to be definitely identified as varicosities, but we reported them as suggestive of varicosities.

The next film is one of the heart. It shows a considerable enlargement of the

heart to the left and a pleuritic reaction covering the left diaphragm and ascending along the right thoracic wall. At an early date, the lung is clear but shows increasing hyperemia and congestion on later films. We see a definite infiltration in the left lung, which persists for a long time.

The colon did not, at the time of examination, show any evidence of the suspected masses. The kidney on intravenous pyelogram showed, on September 5, 1950, a normal kidney pelvis and calyces with some displacement of the ureter in its middle portion. On May 2, 1951, a considerable left sided hydronephrosis

was found. The prostatic gland is enlarged and makes its imprint on the bladder shadow.

Dr. L. Feldman, Cardiologist: The first ECG shows left axis shift, depression of the ST₁ and ST₂ segments, and also depression of ST in AVL. These findings speak for left heart strain. The S is very deep in V₁ and also in V₂, which speak for left heart hypertrophy. V₅ shows depression of ST, corroborating the left heart strain pattern. I don't know when the second ECG was taken, but it is essentially the same, except for the slight increase in the depression of the ST segments mentioned, which could be due to the digitalis that the patient received. Thus, there are two effects — left heart strain and digitalis.

The next ECG shows only slight depression of the ST segments, which may be due to lifting of the strain and/or to elimination of the digitalis effect.

Dr. L. Edidin, Internist: I saw this patient in June, 1951, a few months before he died. At that time, the polycythemia was entirely in the background. We were dealing with a marked anemia and a leukocytosis of about 54,000. We considered the possibility of the anemia being due to a crowding out of the erythroid tissue in the bone marrow by a myeloid hyperplasia and to blood loss, as he had had gastro-intestinal bleeding from time to time.

He entered the hospital on this seventh admission chiefly because of cardiac failure. The question came up as to the etiology of the failure. He had been treated previously for pyelonephritis and hypertension, which could explain his cardiac failure. He was a man of about 55 or 60, I believe, an age when coronary heart disease or arteriosclerotic heart disease is very prevalent. We considered these possibilities. However, the electrocardiogram did not reveal enough specific myocardial or coronary changes to account for the clinical findings of hydrothorax and anasarca.

Secondary amyloidosis to account for the hydrothorax, edema, and clubbing of the fingers in a chronically ill patient sounded very plausible, but a negative congo red test spoke against this diag-

nosis.

We also considered the possibility of pulmonary emboli. Multiple pulmonary emboli can produce cardiac failure (Cor Pulmonale). The electrocardiogram, however, did not reveal right heart strain, as would be expected with pulmonary emboli.

We thus considered the following possibilities: (1) Myeloid hyperplasia crowding out the erythroid tissue; (2) Degenerative or arteriosclerotic heart disease to account for the non-specific cardiac failure; (3) Diffuse kidney disease due to pyelonephritis or leukemic infiltration, as a remote possibility, to account for the edema.

Incidentally, we found a nodule in the rectum. It was a large, fungating mass, very easily felt about 3 or 4 inches up in the rectum. It bled freely and, clinically, appeared malignant on proctoscopic examination. A biopsy, however, did not reveal malignant cells.

Dr. J. M. Greene, Surgeon: A hard fungating, bleeding mass, approximately 2.5 cm. in diameter, was seen in the rectum approximately 4 cm. from the anal margin. Our tentative diagnosis was a fungating carcinoma of the rectum. Because of his very poor condition, we knew that the ideal surgical procedure, an abdominoperineal resection, could not be attempted. We couldn't conceive of fulgurating that mass because of the fear of a stricture so we decided that, if the biopsies would come back positive, we would fulgurate a small area at a time in order to avoid a stricture. Because the two biopsies showed only inflammation, we decided that surgery was not indicated.

Dr. C. Nitka, Resident in Surgery: The first time I saw this man was the time I took the biopsies. At the time of the second biopsy, we had a terrible time stopping the bleeding. It was finally stopped by applying a biopsy forceps with gelfoam against the bleeding point under great pressure. When I saw him the next time, he was on the medical service again. I was called by the Resident in Medicine because the patient had suddenly developed a severe, sharp pain in his right inguinal region while strain-

ing at a bowel movement. When I examined him, he had a large, hard, swollen testis with what felt like a large cord all the way to the external ring. This was extremely tender—and without any bowel sounds. I called the associate on the service. After his examination of the patient, he agreed that the man should undergo surgery. Dr. Harold Cohen, the associate, said that he had never seen anything quite like this. After dissecting off the previous hernia operation, we found a large swollen cord with distended veins. The testis was about four times its normal size, quite hemorrhagic, and edematous. There was no way to stop oozing or to do anything with the testis and cord. We thought the best thing to do for the man at that time was to remove, *in toto*, the testis and cord. In the meantime, there was considerable bleeding in the scrotal sac itself. We controlled this as best we could and sewed the man up. After about five to seven uneventful days, he suddenly "burst open his stitches." The surgical resident was called. He encountered numerous arterial bleeders—apparently there had been no healing at all in the wound. He packed this in an attempt to keep it from bleeding. I saw the patient the next morning. At that time, he was still bleeding through the dressings. I removed those and put on a compression dressing with a pack. He still didn't stop bleeding. Finally, the only way we were able to control the bleeding from this wound (we couldn't tie off the bleeders because the tissue was very fragile) was to pack gelfoam or oxycel into the base of the wound and just tie gauze down into this material with large retention sutures to make a tight pad. Meanwhile, he began to bleed from the site of orchidectomy so that later a stab wound was made for drainage. The wound continued to bleed, would stop for a while and then, when we thought we had it controlled, would bleed again. Bleeding continued off and on up to the time of his death.

Dr. I. Davidsohn, Pathologist: The diagnosis of polycythemia vera was made in this case long before the autopsy. It is interesting to look into the laboratory

findings because they throw some light on the nature of this condition. Most of the time of this patient's stay in the hospital he had no blood picture of polycythemia rubra vera (see laboratory data). The patient actually had an anemia. His highest count here on one occasion was 7.00 million, but even at that time his hemoglobin was only 13.5 gm. This is the picture that one sees in treated, especially successfully treated, cases of polycythemia. As a matter of fact, this state of continued high red blood count associated with a low hemoglobin is regarded as a very satisfactory state in such a patient. Please note that, according to the modern concept of this disease, it is not just a disease of the erythroid elements, but it is a diffuse hyperplasia of *all* the blood elements. In this case, even at the time when the anemia was pronounced, the white cell count was very high, ranging from 40,000 to as high as 80,000. In other words, this is a disease in which there is a diffuse hyperplasia of all bone marrow elements and the corresponding elements found in the peripheral blood. Moreover, in this case there was a high platelet count—up to 1,214,000—as is the rule, even when the red blood count was quite low.

Of course, one could speculate as to why it is that in many cases, especially in those untreated, the red count is the element of bone marrow affected most. There is the possibility that the stimulus, whatever it is, that brings about the hyperplasia exerts its influence in a rhythmic way. One must consider the fact that the normal red cell lives in the peripheral blood for about 80 to 100 days; the normal white cell and the normal platelet, only a few days. If the stimulus which is responsible for the hyperplasia of all the blood elements acts in a rhythmic way—let us say for 3 to 4 days, 5 to 6 days, or 10 days, it is possible that the other elements may not be influenced quite as conspicuously as the red cells because red cells, once produced, will remain in the circulation the normal period of about 80 or 100 days, while the other cells will disappear much sooner. This is just a hypothetical speculation.

In this case, the problem was not that of diagnosis. The problems that presented themselves to the clinician were the question of leukemia and the problem of bleeding, so pronounced as to lead to severe anemia.

A third problem in this case was that of the rectal mass. Was that a cancer, or was it not a cancer? Was it there at all?

Some of these things can be discussed now without going to the autopsy findings. The tendency to bleed is a very common complication of polycythemia. It is difficult to explain because frequently there is not only a normal but an elevated platelet count and also an increased viscosity of the blood. One lacks the factors that usually explain bleeding. In this case, the patient even had an anemia; hence increased blood volume cannot be used as an explanation in this patient. At autopsy, one does encounter markedly distended blood vessels. In this case, distended vessels were found in the stomach and in the lower portions of the intestinal tract. In some cases, perhaps the therapy may have something to do with bleeding. For example, irradiation, especially P^{32} therapy, may have such an influence. Stasis is not a factor, because bleeding occurs in regions where stasis is not known to occur. For example, his nosebleeds could not be explained by stasis.

Patients with polycythemia have a tendency toward fibrosis of the bone marrow. The bone marrow becomes exhausted and fibrosed. But this is not always the case—fibrosis was not present here. There is also a tendency toward leukemic infiltration of the liver. In the literature of about 20 and even 5 years ago, cases were quoted as showing a transition from polycythemia to leukemia. The modern concept is that this is not so. What these patients show is myeloid metaplasia in various tissues (spleen, lymph nodes, etc.). The explanation given that this is secondary to fibrosis of the marrow is not true. For example, in this case there was certainly no fibrosis of the marrow and still there was extensive hematopoietic metaplasia in many parts of the body. This phenomenon

might be explained on the following basis: the same stimulus which acts on the bone marrow acts also on other parts of the reticulo-endothelial system. This is a much better explanation of hematopoietic metaplasia than to say that it is secondary to fibrosis of the marrow.

There is also the question of the diagnosis of polycythemia. One cannot make the diagnosis of polycythemia on the basis of the bone marrow alone. This is the viewpoint I share and have stated in my reports of this case — namely, that the findings were *compatible* with polycythemia, that I could not diagnose it definitely. There are some, however, who claim that one can diagnose it on the basis of certain criteria which they have established. I am not yet convinced that this is correct.

Postmortem Examination

Dr. Davidsohn: Now I would like to show you the findings in this case. In the bone marrow during life were seen some immature red cells of the so-called basophilic megaloblast type (Fig. 1 top), granulocytes (Fig. 1 bottom), megakaryocytes (Fig. 2), and normoblasts—all in increased numbers. In other words, we have here evidence of a diffuse hyperplasia, with special emphasis on erythroid cells in some cases and on megakaryocytes.

The bone marrow from various parts of the body, on postmortem examination, showed no evidence of fibrosis, but rather an active red marrow in the vertebrae, in the sternum, and in the iliac crests (Fig. 3). On microscopic examination, all of these areas exhibited very cellular marrow composed of all elements and tremendous numbers of megakaryocytes. There was not even a trace of fibrosis. In some cases of polycythemia, blood vessels in the lungs and in the bone marrow are described as fibrosed and having thickened walls, thus contributing to and exaggerating the anoxemia. I am not so sure that this interpretation is correct.

Extramedullary hematopoiesis was present in various organs, including the lymph nodes, liver, and spleen, in spite of the fact that there is no evidence of insufficiency of the bone marrow. Exam-

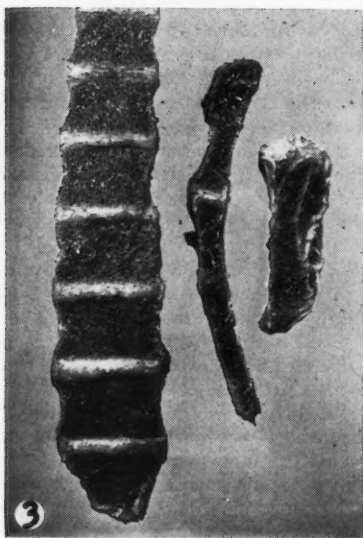
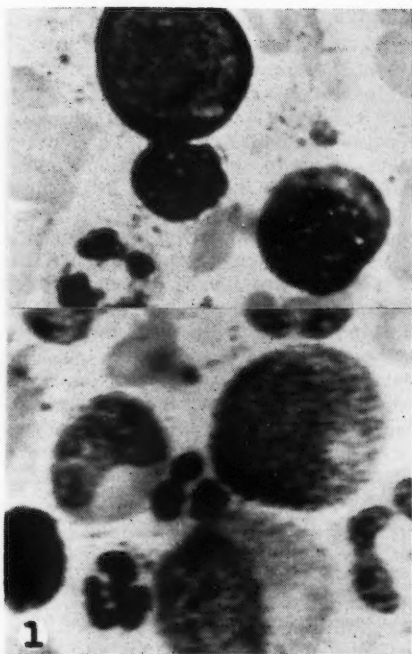


Fig. 1 (top) Bone marrow smear: Very immature blast forms of erythroid cells; (bottom) granulocytes in various stages of development from myelocytes to segmented form. Photomicrograph X1400.

Fig. 2 Bone marrow smear: Megakaryocyte. Photomicrograph X1310.

Fig. 3 Postmortem marrow in the ilium, sternum, and vertebrae was abundant and deep red.

Fig. 4 Enlarged spleen with markedly thickened capsule in polycythemia rubra vera. This organ was also the site of myeloid metaplasia.

ination of a mediastinal lymph node revealed a great many myeloid, as well as erythroid, cells within the structure. The liver also showed similar foci within sinusoids, which often contained increased numbers of megakaryocytes.

The spleen was very markedly enlarged, weighing 1650 gm. (N. 120-150 gm.) (Fig. 4). The capsule was greatly thickened. On section, the spleen showed areas of thrombosis and appeared deep reddish and dry. Thickening of the splenic capsule is a well known finding in patients with polycythemia. On microscopic examination, the parenchyma showed a tremendous increase of connective tissue, fibrosis, and also areas of extramedullary hematopoiesis. Many of the large splenic vein branches were occluded by recent thrombi and the walls of these vessels were thickened. This is another frequent complication in polycythemia.

You will remember that this patient had a complication following his operation for hernia consisting of swelling and pain in the area of the right testis. This complication was due to thrombosis of blood vessels with extensive hemorrhage. These lesions were seen in the surgical specimen of right spermatic cord and testis. About the thrombosed vessels there was inflammatory infiltration. In other words, this complication was due to the same phenomenon that was present in the spleen, namely a tendency toward thrombosis. In this case, it led to a hemorrhagic infarction.

The heart was enlarged, weighing 500 gm. (N. 316 gm.) with some hypertrophy of the left ventricle and marked thickening of the endocardium. There was no evidence of any recent or old infarction.

The liver was enlarged, weighing 2000 gm. (N. 1500-1650 gm.). Microscopically, it showed three changes. There was an extensive passive congestion, in some places actually leading to necrosis. In addition, there was marked atrophy of the hepatic cells in some parts of the hepatic lobule with central necrosis as seen in some cases of acute heart failure. In the sinusoids, there were cells of extramedullary hematopoiesis, especially megakaryocytes, in tremendous num-

bers.

Summarizing the findings so far, then, I believe this is a typical case of polycythemia vera with the usual course, eventually leading to anemia, with complications due to thrombosis and bleeding, and without leukemia. There was myeloid metaplasia, but not leukemia. I am inclined to agree with those who say that most cases of leukemia complicating cases of polycythemia have been misdiagnosed. I think that it is due to misinterpretation of the results of myeloid metaplasia. The spleen and other organs become the sites of myeloid metaplasia and these immature cells get into the peripheral circulation. However, this does not hold for those cases in which acute leukemia does complicate polycythemia. These cases have been observed but, as far as I can tell from the literature, most of these cases occur in patients who have been treated with irradiation—especially with radioactive phosphorus.

In the rectum, we found a perfectly smooth mucosa, no masses, and no ulcerations. This confirms our findings of hemorrhage, thrombosis, and inflammation in the two biopsy specimens. In other words, I suspect that the rectal mass seen was due to a thrombosis of one of the hemorrhoidal veins. There certainly is no evidence of past or present tumor. As to the rest of the gastrointestinal tract, the mucosa was intact although an almost varicose kind of dilatation of the superficial mucosal vessels was noted in the upper portion of the stomach and in various parts of the intestinal tract.

Anatomic Diagnosis

Polycythemia rubra vera with extramedullary hematopoiesis (myeloid metaplasia) of the spleen, liver, lymph nodes, and adrenals (medulla). Thrombosis of the intrasplenic branches of the splenic vein and of the right spermatic vein (surgical specimen S-2639-51). Concentric hypertrophy of the left ventricle of the heart with congenital absence of the circumflex branch of the left coronary artery. Bilateral hydrothorax, hydropericardium, and moderate ascites. Subdural and intradural hemorrhage of the menin-

ges (old right pachymeningitis hemorrhagica interna). Edema of the cerebrum and cerebellum. Acute passive congestion of the pituitary. Edema of the lower extremities. Arteriosclerosis of the aorta. Acute focal bronchopneumonia, acute and chronic passive congestion, and atelectasis of the lungs. Acute passive congestion and central necrosis of the liver. Nephrolithiasis, acute passive congestion, and arterio- and arteriosclerosis of the kidneys. Cyanosis of the skin.

Cause of Death: Left heart failure in polycythemia rubra vera (late stage).

Summary and Discussion

Dr. L. Edidin: How do you account for the anasarca that this patient had? We could not explain it. I was not quite satisfied that it was on a cardiac basis. I think that is what I said on the chart.

Dr. I. Davidsohn: Don't you think that anasarca could be due to cardiac failure in a patient with hypertension, an enlarged heart (500 gm.), and anemia? I think the edema can be explained on the basis of anemia with resulting anoxia in a patient with hypertension and an enlarged heart.

Dr. M. Kirshen, Internist: What were the changes in the liver?

Dr. Davidsohn: The changes in the liver were those of passive congestion in the very late stages with central necrosis and atrophy of some of the cords.

Dr. I. A. Rabens, Internist: What would you say about the associated hypertension? Is it coincidental in most cases or a result or part of the picture of polycythemia?

Dr. Davidsohn: Hypertension has been described in some patients with polycythemia. The opinions regarding this type of hypertension are varied. I don't know that it is essentially a part of the picture, but there is a form of polycythemia frequently associated with hypertension.

Dr. Rabens: I wonder whether the majority of them are associated with hypertension due to the viscosity of the blood.

Dr. Davidsohn: It would be difficult to explain in a case like this, in which there was actually an anemia rather than an

erythremia. Here, the increased blood viscosity may have been present temporarily but it certainly did not persist when anemia developed.

Dr. Rabens: I don't understand the biologic need for extramedullary hematopoiesis in the absence of fibrosis of the bone marrow.

Dr. Davidsohn: I tried to explain that, but perhaps it was not clear. The usual concept is that, as a result of fibrosis of the bone marrow, the other process is compensatory. I don't agree with that, because, as in this case, there is no fibrosis of the bone marrow and yet there was metaplasia. Therefore, I suggest that the same stimulus which produces hyperplasia in the bone marrow may also produce hyperplasia in the other parts of the body — in some individuals more than in others. What this stimulating agent is, we don't know.

Dr. Edidin: Two and a half years ago, when I first saw this patient, he did not have a generalized anasarca or anemia. Could hypoproteinemia explain the hydrothorax? Could the hydrothorax be due to the heart failure?

Dr. Davidsohn: Of course, you saw in the liver that he had right heart failure. He had it terminally. How long he had it, I don't know. The liver weighed 2000 gm. Would you say that you cannot explain the phenomenon of anasarca in an individual with a red count of 2.50 million and with hypertension and a failing heart?

Dr. Edidin: He had no hypertension at the time I saw him.

Dr. Davidsohn: According to the clinical abstract here, there was evidence of hypertension.

Dr. Edidin: How about the blood pressure 3 or 4 years ago?

Dr. Davidsohn: I don't know. I can only say that anatomically I think it can be fully explained by the autopsy findings.

Dr. L. Feldman: An interesting thing is that the first electrocardiograms showed some degree of heart strain. The second tracings showed a little more strain, and and it was thought there was perhaps an additional effect of digitalis. The third ECG showed no heart strain at all.

What I want to bring out is this: that heart strain is fluctuant and heart strain is reversible; heart strain means nothing anatomical. When you see ECG's in practice from week to week, you can realize what has happened here, too. No doubt, the man had myocardial hypertrophy. There is no doubt about the anemia or about the fact that at one time or another he had hypertension. There is also no doubt that at one time or another he had heart strain and heart failure. I believe that we could account for the heart strain by a combination of factors acting upon his heart muscles.

Dr. Davidsohn: I would like to mention another finding, which may have some bearing on the present discussion. Although the coronary orifices were normal in appearance, the circumflex branch of the left coronary artery was absent. The right coronary artery supplied the posterior wall of the left ventricle. Dr. Luisada, do you think that such a heart is handicapped, and can you tell us something more about this condition?

Dr. A. Luisada, Cardiologist: I don't think that this would mean much in this case. These congenital anomalies are present from birth. If they represent a handicap, they are revealed much sooner in life. We know that, in some individuals, much more blood is given by the left coronary and, in some, much more by the right coronary. It is well to have a complete balance between the two vessels. I don't think that this case is

anatomically handicapped.

Dr. Feldman: May I add that in about 4-6% of patients the right coronary artery supplies the posterior wall of the left ventricle and the left circumflex branch is missing.

Dr. Kirshen: Was there any evidence of hemosiderosis? The man had so many transfusions.

Dr. Davidsohn: No, there was no hemosiderosis. And that is very interesting. In a recent report on that subject, it was pointed out that patients with polycythemia do not show hemosiderosis under circumstances where they would otherwise be expected to show it. I remember a case treated with phenylhydrazine that led to hemolysis, in which there was hemosiderosis. I think that with phenylhydrazine, hemosiderosis has been noted, but otherwise it is rather noticeable by its absence.

REFERENCES

- (1) Rosenthal, N. and Bassen, F. A., Course of Polycythemia, *Arch. Int. Med.* 62:903-917, 1938.
- (2) Berlin, N. I., Lawrence, J. H. and Gartland, J., Blood Volume in Polycythemia as Determined by P³² Labeled Red Blood Cells, *Am. J. Med.* 9:747-751, 1950.
- (3) Lawrence, J. H., The Control of Polycythemia by Marrow Inhibition, A Ten Year Study of 172 Patients, *JAMA* 141:13-18, 1949.
- (4) Schwartz, S. O. and Ehrlich, L., The Relationship of Polycythemia Vera to Leukemia; a Critical Review, *Acta Haematologica* 4 (Fasc. 3): 129-147, 1950.
- (5) Block, M. and Jacobson, L. O., Myeloid Metaplasia, *JAMA*: 1390-1396, 1950.

CARDIAC NEUROSES—

(Continued from page 7)

physical therapies, or other remedies are actually obtained through suggestion. This is possible only if the doctor approaches his patient with sympathy and believes in the remedy he is prescribing and if the patient fully cooperates with the doctor.

A complex mechanism which acts

through basal ganglia, autonomic fibers, and hormones, may unconsciously contribute to the treatment of many disorders of the heart and vessels. On the other hand, pharmacologic and physical treatment of basic cardiovascular disorders may contribute to better mental equilibrium in many cases where a psychic disorder was symptomatic, secondary, or somehow connected with one of the many diseases of the heart or vessels.

BOOK REVIEWS

PRINCIPLES OF REFRACTION by S. J. Beach, A.B., M.D., F.A.C.S. Cloth. First edition. 158 pages with 18 figures. St. Louis, The C. V. Mosby Company. 1952. \$4.00.

Although there are many elaborate volumes on this subject, this new book probably is one of the simplest, clearest and most practical. The author begins with basic ideas and draws upon familiar illustrations and advances from them in orderly stepwise fashion. It is necessary only to possess a knowledge of basic physiology, anatomy of the eye, and college physics for an understanding of the material. In addition to the discussions on refraction, there is an informative chapter on ocular neuroses.

NITROUS OXIDE-OXYGEN ANESTHESIA by F. W. Clement, M.D. Cloth. Third Edition. 369 pages with 129 illustrations. Philadelphia: Lea and Febiger, 1951. \$6.50.

This book is probably the most complete and is the only work devoted solely to Nitrous Oxide-Oxygen anesthesia. This subject is covered in great detail and includes the advances made in this field since publication of the last edition. The most important advances—entailing the use of curare as an adjunct to all inhalation anesthesia, is accurately described in detail. Other subjects brought up to date are the dangers associated with prolonged oxygen deficiency, the more detailed method of inhalation anesthesia administration, mechanism and treatment of shock and the role of carbon dioxide and that of the sino aortic areas in the protection of the body in lowered oxygen intake. The chapter on dental anesthesia has again been expanded to include the advances pertinent to this phase of the subject. This volume should be in the library of all anesthesiologists and should also be included in all medical libraries.

REACTION TO INJURY. By Wiley D. Forbus, M.D. Cloth. First Volume: 797 pages, 520 illustrations, 1943. \$9.00. Second Volume: 1110 pages, 836 illustrations, 1952. \$20.00. First Edition. Baltimore: The Williams and Wilkins Co.

These two volumes approach the field of pathology from a dynamic viewpoint in keeping with the most recent concepts of medical study. The result is a comprehensive study of the individual as a whole who reacts to changes in environment: "(1) by resisting, (2) by submitting, and (3) by effecting an adaptation." As a result, the volumes become a textbook of pathology for medical students and physicians which encompasses all the classical work in the field and applies to it newer concepts. The book does not divide the subject into "general" and "special" aspects, but studies it as a whole—a refreshing and noteworthy approach. The second volume, since the first deals with reaction by "resisting," deals with reaction by "submitting and adapting." Together, they integrate all fields of medicine and science into the heart of pathology. The net result is a magnificent two-volume text of

pathology which serves as an excellent and mature textbook and a superbly written reference for the entire field.

INHALATION ANESTHESIA A FUNDAMENTAL GUIDE by Arthur E. Guedel, M.D. Cloth. Second Edition. 143 pages with 6 charts. New York: The Macmillan Company, 1951. \$3.75.

This book is a general discourse on the administration of inhalation anesthetics. Intended for the general practitioner who may occasionally be called upon to administer some form of inhalation anesthesia or for the medical student who is taking a didactic course in anesthesiology, this book covers in a general and fairly superficial way, the principles of inhalation anesthesia. A novel feature of this book is the segregation into a separate section, which composes more than half the book, the subject of Anesthetic Accidents. This helps focus the attention of the reader to them and perhaps aids in their prevention. However it should be stated that the discussion of ventricular fibrillation and sudden cardiac arrest is hopelessly outdated and the pessimistic views contained therein have been definitely disproven. A subsequent edition of this book may be useful to medical students taking a didactic course in anesthesiology and can be recommended to them.

BONE TUMORS by Louis Lichtenstein, M.D. Cloth. First edition. 315 pages with 155 illustrations. The C. V. Mosby Company; St. Louis. 1952. \$10.50.

This new book is based largely upon original papers by the author and Dr. Henry L. Jaffe which are widely acclaimed. It is probably the best available practical work on bone tumors. The author presents a very logical classification of bone tumors about which the discussions are oriented. The book is very readable and the text is amply illustrated with beautiful roentgenograms and photographs of tissue sections and gross specimens. Accepted principles of therapy are stressed, although controversial material is not omitted. There is little emphasis upon surgical technic. The bibliography, though not extensive, is selective and adequate. This work should be of great practical value to general practitioners, radiologists and orthopedic surgeons.

TEXTBOOK OF HISTOLOGY by Alexander A. Maximow and William Bloom. Cloth. 616 pages with 986 illustrations. Philadelphia and London: W. B. Saunders Co. Sixth Edition, 1952. \$20.00.

This well known and classical text has been remarkably expanded in order to include the tremendous advances in histological research during the past four years. In order to do this, the more basic concepts have been condensed with great clarity, and the result is a text which reads smoothly and presents its material concisely. Revised chapters and sections and new illustrations and plates add further to the quality of the

text. Of particular note is the new introductory chapter by Professor W. L. Doyle, "which integrates the submicroscopic, biochemical and enzymatic constitution of cells," the new chapters by Dr. I. Gersh on "The Endocrine Glands," and the material dealing with connective tissue by Professor P. P. H. DeBruyn. One cannot help but realize that this sturdy text has been strengthened once again and it is highly recommended to the student and practicing physician in need of an up-to-date text or reference book in his-
tology.

TEXTBOOK OF PHARMACOLOGY by William T. Salter, M.D. Cloth. First edition. 1240 pages with 284 page figures. Philadelphia and London: W. B. Saunders Company, 1952. \$15.00.

This new textbook of pharmacology is certainly one of the most valuable books published in 1952. The author is a physician and has a keen appreciation of the needs of the medical student and practitioner. His approach to the subject is dynamic and clinical. He has a bright sense of humor and a most refreshing style. Wherever known, the mechanism of drug action is discussed in regard to correction of the pathologic physiology produced by disease processes. This logical method is much more meaningful than the empirical approach and certainly more scientific. The material is very current. Most of the modern antibiotics, chemotherapeutic drugs, antihistamines, amebicides, antimalarials and hormones are thoroughly discussed as to chemistry, mode of action, indications, dosage, toxicity and therapeutic efficacy. The book is carefully organized, interesting, scientific and complete. It is a textbook of medical pharmacology and is most highly recommended for medical students and practicing physicians.

PHYSICAL DIAGNOSIS by Harry Walker, M.D., F.A.C.P. 461 pages with 126 illustrations. St. Louis: C. V. Mosby Company. First Edition. 1952. \$8.00.

This first edition book concerning perhaps the most important single diagnostic method in medicine is certain to find an eventual place on most medical shelves. There are a great number of choicely-picked illustrations which enhance the value of this book—especially to the neophyte, since a goodly number of illustrations will be familiar to the physician as a part of his everyday practice. Although there is very little new material in this book, it is organized in a logical manner, and tends to be somewhat more comprehensive than most standard references on the subject; yet it avoids verbosity, and retains a highly commendable readability.

Gene Mason

INTERNAL MEDICINE. Edited by Michael G. Wohl, M.D., F.A.C.P. Cloth, 1563 pages, 236 illustrations. Philadelphia: Lea and Febiger. Fifth Edition. 1951. \$15.00.

This text in internal medicine is designed for the medical student and general practitioner and is a concise, well-written book. The basic sciences are well integrated into the presentation of the disease entities. Such features as chapters on rehabilitation, psychosomatic medicine, and the general adaptation syndrome enable the book to achieve a study of the patient as a "whole," as modern medicine stresses today. The sections on therapy are quite recent, enabling the practicing physician—and student—to get a clear picture of recent advances in therapeutics that have been proven of worth after adequate clinical trial. The book is easily read and is recommended to the student and physician as a ready text for all phases of internal medicine.

ABSTRACTS SECTION

CLARK, GEORGE and GOLDBERG, S. E. Visual Disturbance as a Sequel to Unilateral Frontal Lesions in the Rat. *J. Comp. & Physiol.* 44:487-491, 1951.

It was possible to show that after a small unilateral frontal lesion, disturbances in vision often occur. When this operation is performed in blinded rats, approximately 50 per cent show the same gross behavior changes as are seen in normals. This suggests that other factors than vision are possibly responsible.

CONGDON, E. D. Useful Pressure Exchanges Between Human Voluntary Muscles and Their Environment as Their Second General Mechanical Function. *Anat. Rec.*, v. 112, no. 2, February 1952. Paper presented at the American Association of Anatomists, Providence, R. I., March 19-21, 1952.

Certain useful pressures of human voluntary muscles are familiar in medicine. Many of them seem never to have been clearly recognized. No general appraisal and classification of them

could be found in anatomical or physiological literature.

Muscular pressures are divisible into three groups: (1) those aiding visceral functions, (2) pressure exchanges with the outside world, and (3) pressures which assist the familiar tension between origin and insertion.

Many human voluntary muscles exhibit two kinds of pressure functions. It is not very rare for a muscle to possess three varieties. No muscle was found without at least one type. It is claimed then that pressure exchange is a general property of these muscles.

A naming of the two functions is desirable. The familiar tension between origin and insertion is here said to carry on longitudinal action and the pressure exchange, lateral action.

Lateral actions assure all or nearly all human voluntary muscles a visceral use.

Lateral actions are necessary for the maintenance of many mechanical functions of the body.

KOENIG, H.: The influence of alkalosis on retrograde degeneration of nerve cells. The Anatomical Record, Vol. 106, No. 2, Feb., 1950.

Acute alkalotic tetany is associated with an increase in cytoplasmic basophilia of neurons (Koenig, '49) and with an increased cytoplasmic absorption of ultraviolet light at 2537 Å° (Koenig and Koenig, unpublished data). This is interpreted as an increase in ribonucleic acid.

Male guinea pigs of like age were employed in this study. Experimental animals were administered 6 cc of a 10% solution of sodium carbonate by gavage twice daily. Blood pH was determined periodically. After a preliminary period of alkalosis, the left sciatic nerve was cut at the level of the ischial tuberosity in these and in control animals. The former were continued on sodium carbonate until sacrifice. Blood pH was maintained between 7.55 and 7.80. No manifest tetany was seen. Fixation was effected by vascular perfusion with 10% formalin-saline-gum acacia, and the sacral spinal cords stained with thionin buffered at pH 3.25.

To date, sacral cords up to 10 days after nerve transection have been studied. At 48 hours no indication of retrograde degeneration was seen in control or experimental cords. Five days after transection, the control cord showed neurons in early stages of retrograde degeneration, but the experimental cord showed advanced changes. At nine and ten days, retrograde degeneration was moderately advanced in control animals, but markedly pronounced in alkalotic animals.

KOPPER, PAUL H. The Reducing Power of Bacterial Cells. Bact. Proc., 71, 1951.

A strain of *Escherichia coli* was selected for studying the reduction of nitrate and methylene blue by bacterial cells. The organisms were grown in nutrient agar at 37°C. No enhancement in nitrate reducing activity was noted with bacteria cultivated in a 1% NaNO₂ nutrient agar medium. Nitrate reduction was found to be independent of substrate concentration but markedly accelerated with increasing cell concentration. Exposure to various pH levels from 4 to 11 did not affect the reducing power of the bacteria toward the two substrates nor their viability. Pretreatment of 18 hour old bacterial cultures with 50 per cent veal infusion broth for one hour, followed by centrifugation and washing, considerably increased the rate of nitrite production and methylene decolorization by the organisms. Identical results were obtained with cultures grown for 3, 4 and 5 hours, the youngest being the most active. Cultures of *E. coli* grown at 43°C for 18 hours showed a markedly decreased ability to reduce the substrates. About one mg. of NaNO₂ was produced by 2×10^{10} *E. coli* in 20 hours at 37°C. Such organisms did not differ from controls in viability and polysaccharide content. The nature of the reductant remained undetermined. Among other bacteria tested, members of the genera *Pseudomonas* and *Chromobacterium* proved to be the strongest nitrate and methylene reducers; a number of gram-negative rods, *Staphylococcus aureus* and *Corynebacterium xerosis* were less

active; *Streptococcus pyogenes* and *Clostridium perfringens* displayed hardly any reducing ability.

LUISADA, ALDO A. Therapy of Paroxysmal Pulmonary Edema by Antifoaming Agents. Proc. Soc. Exp. Bio. & Med., 74:215, 1950.

Experiments were performed with anti-foaming agents by inhalation in rabbits in order to decrease the severity of pulmonary edema caused by a standard dose of intravenous adrenalin. Poorly volatile drugs (heavy alcohols, Span 85) failed to exert any favorable action. This action is partly due to the anti-foaming property of alcohol and partly to its action on the central nervous system. Combination of parenteral morphine with alcohol by inhalation gave the best results.

ROTHMAN, A., RAPOPORT, L. P., and DAVIDSOHN, I. Carcinoma of the Cervix in Jewish Women. Am. J. Obst. & Gynec., 62:160-162, 1951.

The incidence of carcinoma of the cervix has been analyzed in Jewish and non-Jewish admissions to the Mount Sinai Hospital of Chicago for a 10-year period. During this period there were 29 cases of carcinoma of the cervix of which seven cases (24.1 per cent) were in Jewish patients and 22 cases (75.9 per cent) were in non-Jewish patients. The total female admissions were 36,759 Jewish patients (74.4 per cent) as opposed to 12,648 non-Jewish patients (25.6 per cent). Statistically, carcinoma of the cervix in this series was found to be nine times more frequent in non-Jewish patients.

In the same series, carcinoma of the corpus uteri did not show a statistically significant difference.

The pertinent literature is briefly reviewed, which relates to the etiologic significance of circumcision and race with relation to carcinoma of the cervix.

SAIDEL, LEO J., and GOLDFARB, A. ROBERT: Ultraviolet Absorption Spectra of Peptides and Amino Acids, (presented at the meeting of the Federation of American Societies for Experimental Biology in Cleveland, April 30, 1951).

By making minor changes in the Beckman Spectrophotometer and by correcting for stray radiation, it is possible to use this instrument for the study of spectra of compounds in the ultra violet region from 200 mμ to 230 mμ: A study of the spectra of peptides and amino acids has revealed striking quantitative differences between these two groups of compounds.

SMITH, J. A. The Bronchoconstrictor Effects of Thiamine. Presented before The Chicago Society of Allergists, March, 1951.

A review of the toxic effects of thiamine when given to human patients was presented. One effect is bronchoconstriction. In experimental animals, some bronchoconstriction may be shown to be due to liberation of histamine; it is possible that some or all of the toxic effects in humans caused by injections of thiamine might be due to liberation of histamine.

SCHOOL NOTES AND NEWS

PRESIDENT SHEININ HONORED BY PHI LAMBDA KAPPA

At their annual Senior Dinner-Dance on May 24, at the Furniture Club of America, the Alpha Rho Chapter of the Phi Lambda Kappa Fraternity presented their First Annual Gold Medal Award to President John J. Sheinin. This award was created by The Chicago Medical School chapter of Phi Lambda Kappa to be presented annually to the individual whose loyal and devoted service to The Chicago Medical School has contributed most to the school's growth and development and whose efforts have helped increase the stature of the school.

In presenting the award to Dr. Sheinin, Sanford Cohen, the president of the Alpha Rho Chapter, said that Dr. Sheinin "clearly stands out as the central figure in the drive to create and perpetuate the ideals and purposes of The Chicago Medical School. His loyalty, devotion, sacrifices, and efforts have been the keynote in the growth of The Chicago Medical School. He has almost single-handedly brought recognition, honor, prestige, and integrity to The Chicago Medical School."

In accepting the award, Dr. Sheinin said that he regarded the Medal not as a reward for past achievements, but rather as an obligation for future efforts. He promised to continue his untiring efforts on behalf of the school and to work constantly to achieve the great goals which have been set for the school.

The QUARTERLY proudly notes the appointment of Dr. Jerome S. Tobis, class of 1943, as Associate Professor of Medicine and Director of the Department of Physical Medicine and Rehabilitation of the New York Medical College, Flower and Fifth Avenue Hospital.

Dr. Tobis was one of the founders and the first editor of The QUARTERLY.

NEW APPOINTMENTS

President John J. Sheinin has announced the appointment of Dr. James G. Shaffer as Professor and Chairman of the Department of Microbiology and Public Health.

Dr. Shaffer earned his Bachelor of Science degree at Manchester College and his degree of Doctor of Science at Johns Hopkins University. He has taught at Johns Hopkins School of Hygiene and Public Health as Instructor in Immunology and Filterable Viruses and at Vanderbilt University School of Medicine as Assistant Professor of Preventive Medicine and Public Health. During the war, Dr. Shaffer was on active duty for three years and was discharged in 1946 with the rank of Major in the Sanitary Corps. More recently, he has served as Director of Laboratories and Consultant in Microbiology at Louisville Children's Hospital.

Dr. Shaffer has engaged in extensive research studies in the field of Microbiology and Public Health and is the author

It is with a sense of profound sadness and a feeling of deep loss that the QUARTERLY announces the death on June 15, of Dr. Howard L. Sloan. Dr. Sloan was drowned when the canoe he was in capsized in the rapids of the Des Plains River.

Dr. Sloan was graduated from The Chicago Medical School in 1942. He served in the Army Medical Corps during World War II as a captain. Upon his discharge, he returned to The Chicago Medical School where he served as Student Health Officer before being appointed a Research Fellow in the Department of Physiology. Recently, he was on leave for graduate work at the University of Chicago Medical School.

The student body, Faculty, and Alumni extend their heartfelt sympathy to his widow, Mrs. Lillian Sloan, who is the President of the Faculty Wives Association.

or co-author of some twenty articles which have been published in the American Journal of Hygiene and other scientific journals.

* * * *

The following new appointments to the faculty have also been announced by the Office of the Dean:

Dr. E. W. Fischman, Professor Emeritus of Gynecology and Obstetrics, upon his retirement as Professor and Chairman of that department on September 31, 1952.

Dr. Leonard B. Nice, Professor Emeritus of Physiology and Pharmacology, ^{Department of} Professor and Chairman of that department on September 31, 1952.

Dr. Aaron Grossman, full time Assistant Professor of Pediatrics.

Dr. Morris A. Kaplan, Assistant Professor of Medicine.

Dr. Meyer J. Barrash, full time Instructor in Medicine.

Dr. Samuel B. Broder, Assistant Professor of Neurology and Psychiatry.

Dr. E. Lewin Arendt, Instructor in Surgery.

Dr. Alex M. Berman, Class of 1936, Assistant in Otolaryngology.

Dr. Olga M. Haring, Assistant in Medicine.

Dr. Wai-Chi Liu, Instructor in Surgery.

Dr. Arthur A. Miller, Instructor in Psychiatry.

Dr. Thomas J. Gully, Assistant in Otolaryngology.

Dr. Regina Schoental, Associate in Oncology.

Dr. Reuben H. Segel, Assistant in Psychiatry.

Dr. Antonio N. Silvetti, Fellow in Surgery.

Dr. Luigi Tagliacozzo, Associate in Psychiatry.

Dr. Starks J. Williams, Assistant in Pediatrics.

Dr. Ernest B. Zeisler, Associate in Medicine.

FACULTY NEWS

Department of Anatomy

Six doctors and two assistants in the Department of Anatomy participated in the program of the American Association of Anatomists which was held in Providence, Rhode Island. The participating members were Drs. George Clark, E. D. Congdon, Hans Elias, Harold S. Fish with assistant Jack Gilman, Dr. Harold Koenig with assistant Donald Feldman, and Dr. Leon H. Strong.

Congratulations to Dr. Hans Elias who has been awarded the Dr. M. L. Parker Award which is given upon recommendation of the Faculty to a member of the Staff for meritorious scientific research during the academic year.

Dr. Harold Koenig has received from the United States Public Health Service \$5,200 as a renewal and expansion of a grant for study of nucleoprotein metabolism in living nerve cells grown in tissue culture.

Department of Medicine

Dr. Aldo H. Luisada has received two grants totalling \$7,140 from the Chicago Heart Association for continuation of his research studies of cardiac function.

Dr. Luisada spent part of the summer in Italy, where he presented several lectures and was awarded honorary membership in the Piedmontese Academy of Surgery.

Dr. A. B. Rimmerman has been appointed chief consultant in Cardiology for the entire Fifth Army Area.

Dr. Hugo R. Rony has been appointed Attending Physician in Metabolism and Endocrinology at Mount Sinai Hospital, Chicago.

Dr. K. K. Datey has been engaged in research studies in the Laboratory of Cardiology which is under the direction of Dr. Aldo A. Luisada, Associate Professor of Medicine and Program Director of Cardiology. Dr. Datey, a prominent cardiologist from India, carried out postgraduate studies in London, England, following receipt of his degrees from the University of Bombay.

Department of Microbiology

Dr. Harold Elishevitz has been elected Chairman of the Program Committee of the State Microscopic Society of Illinois.

Department of Obstetrics

Dr. Irving Siegel has been elected a member of the American Federation for Clinical Research.

A testimonial dinner in honor of Dr. Egon Walter Fischmann, who is retiring from active teaching and administration of the Department of Obstetrics and Gynecology, was held June 11, 1952, at the Hotel Sherman.

Department of Pathology

Dr. Israel Davidsohn, Dr. Elie P. Leroy, and Dr. Russell Milliser presented a demonstration at the American Medical Association Convention in Chicago.

Dr. Israel Davidsohn has completed a tour of duty as Resident Consultant, Armed Forces Institute of Pathology, Washington, D. C.

Dr. Kurt Stern has been elected a Fellow of the American Association for the Advancement of Science and has been appointed Contributing Editor of the American Journal of Clinical Pathology.

Dr. Israel Davidsohn, Professor and Chairman of the Department of Pathology, and Pathologist and Director of Laboratories, Mount Sinai Hospital, has received a renewal of \$13,068 from the United States Public Health Service for a continuation of his studies of "Natural and Immune Antibodies in Inbred Mouse Strains with Low and High Tumor Incidence."

Department of Physiology

Dr. Piero P. Foa has received a grant of \$6,000 from Eli Lilly and Co. for continuation of his work on experimental diabetes and the hyperglycemic factor. Dr. Foa was in Paris this past summer to present two papers before the Second International Congress of Biochemistry. These papers were entitled: "The Effect of Insulin-Free Pancreatic Extract on Blood Ketones" and "Extraction and Physiological Functions of the Hyperglycemic Factor of the Pancreas."

Dr. Piero P. Foa presided as Chairman

of one of the Endocrinology sessions at the recent meeting of the American Physiological Society in New York. He has also been elected Councillor to the Chicago Section of the American Federation for Medical Research.

Dr. Leonida Santamaria has been appointed Visiting Research Fellow at the Sloan-Kettering Institute in New York City. Dr. Santamaria is a Fullbright Fellow who has been at The Chicago Medical School for the past year.

Department of Psychiatry

Dr. Rudolph Dreikurs, Professor of Psychiatry, has been elected President-Elect of the American Society for Group Psychotherapy and Psychodrama.

Department of Surgery

Dr. Joseph T. Gault delivered two papers at the Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine. These lectures were for the Staff and the visiting students and scientists and were entitled: "The Life History of Clinical Cancer" and "Basic Problems in Cancer as Viewed by the Clinician."

Dr. Emanuel Marcus, Associate in Surgery, has been awarded the Chicago Surgical Society Prize for 1952 for his research work on "Homologous Heart Grafts."

Dr. Philippe Shubik, Assistant Professor of Surgery and Coordinator of Oncology, has received a renewal of \$25,000 from the National Cancer Institute to be used for cancer teaching, and \$5,000 as the second payment of a grant from the same source for "Study of Successive Stages of Carcinogenesis."

The Cancer Control Branch of the United States Public Health Service has made a new grant of \$22,518 to Dr. Philippe Shubik for investigating industrial and environmental agents concerned in the production of cancer.

Dr. Caesar Portes has been elected Secretary-Treasurer of the North Side Branch of the Chicago Medical Society.

Dr. Donald S. Miller, Professor and Chairman of the Department of Orthopedic Surgery, was invited to present several lectures and clinics while on a trip to South America this summer.

ALUMNI NEWS

Class of 1910

The staff of the *QUARTERLY* notes with regret the death of Dr. E. E. Collins on May 16, 1952. Dr. Collins was for many years chief physician for Swift & Company.

Class of 1943

Congratulations to Dr. Abraham Schwartz, Staff Psychiatrist at the Brentwood Veterans' Administration Neuropsychiatric Hospital, Los Angeles, and his co-worker Dr. J. H. McLellan of the same hospital. They have been awarded the Trudeau Prize for work on "The Treatment of Tuberculosis Patients with Electroshock Therapy."

Class of 1944

Dr. Vincent C. Sarley was awarded the degree of Bachelor of Laws on June 16, 1952. Congratulations!

Class of 1946

The *QUARTERLY* recently received a highly gratifying letter from Dr. Marvin F. Loring. We were impressed by this letter not only because of the nice things which Dr. Loring had to say about The *QUARTERLY*, but because he took the trouble to write to us in order to keep us informed of his plans. Dr. Loring reports that he has completed his second year of residency in radiology at the Hospital of St. Raphael in New Haven, Connecticut, and is at present preparing to leave for a year of study at the Royal Cancer Hospital of London, England, where he will specialize in radiotherapy of cancer. He is undertaking this work under a British-American exchange fellowship in cancer research which is sponsored jointly by the American Cancer Society and the British Empire Cancer Campaign.

Class of 1947

Congratulations to Dr. and Mrs. Frank Rampello on the birth of their daughter, Isabella, on June 28, 1952.

Class of 1948

Dr. Harvey Lozman announces that he has opened an office at 220 Sterling Place in Brooklyn, New York. The *QUARTERLY* wishes Dr. Lozman the very best of luck.

Class of 1950

Dr. Herbert Fishbein has been appointed Senior Resident in Radiology at Maimonides Hospital in Brooklyn.

Dr. Joshua Magidsohn is now serving a residency in Internal Medicine at the Veterans' Administration Hospital, Hines, Illinois.

Dr. Lenard D. Grayson announces that he has opened an office at 380 East 46th St., Brooklyn, New York.

Congratulations to Dr. William W. Anderson on his marriage to Mary Elizabeth Franklin on July 4, 1952, in Kobe, Japan.

Congratulations to Dr. and Mrs. M. J. Sherman, Jr., on the birth of their daughter, Sandra Meta, on July 12, 1952.

Congratulations to Dr. and Mrs. Melvin Ehrlich on the birth of a daughter, Stella Beth, born April 16, 1952.

Class of 1951

Congratulations to Dr. and Mrs. Lester Cohn on the birth of a son, Martin Jerome, on February 15, 1952. Dr. Cohn has recently accepted a residency in Medicine at the Veterans Administration Hospital in Los Angeles, California.

Dr. Sanford I. Gaylord has been appointed Resident in Internal Medicine at the Veterans Administration Hospital, Dearborn, Michigan.

Dr. Walter Charles has accepted a Residence in Pediatrics at the Syracuse Memorial Hospital, after having finished his internship at Kings County Hospital of New York.

Dr. Morton Doblin, having completed his internship at Cook County Hospital is now on the staff of the Michael Reese Hospital as a Resident in Pediatrics.

Dr. Franklin Friedman has been appointed Resident in Surgery at Mount Sinai Hospital, Chicago, following the completion of his internship at Bronx Hospital, New York.

Dr. Arthur Lisbin has accepted a Residency in Pediatrics at the Metropolitan Hospital, New York City, following completion of an internship at Kings County Hospital, New York.

Dr. Jerome Podgers has been appointed to the Resident staff in Internal Medicine at the Veterans' Administration Hospital, Hines, Illinois. Dr. Podgers served his internship at Cook County Hospital.

STUDENT NEWS

Senior Class

Best wishes to Ed Berkwits on his marriage to the former Miss Gloria Kozin (M.D.) on June 24, 1952.

Mr. and Mrs. Dan Colburn announce the birth of their son, Bruce William, on August 9, 1952. Congratulations!

We wish to congratulate Harold Fischer on his marriage to the former Miss Annette Cohan of Newark, New Jersey, on June 22, 1952.

Congratulations to Mr. and Mrs. Jerome Handler on their marriage on June 29, 1952. Mrs. Handler is the former Miss Barbara Levin of Chicago.

Lesther Winkler has announced his engagement to Miss Charlotte Siedband of Chicago, Illinois. Les and Charlotte are planning the wedding for next June.

Congratulations to Marvin Kranis on his engagement to Miss Elaine Frank of Brooklyn, New York.

Junior Class

Best wishes to Meyer Blatt on his engagement to Miss Rosalind Wallach of the Bronx, New York.

Congratulations to Edward Etzel on his engagement to Miss Ruth Eagleson of Pittsburgh, Pennsylvania.

We offer congratulations to Bill Kalt on his engagement to Miss Lora Leventhal of New York City.

Congratulations to James McMeel on his engagement to Miss Joan Getzinger of South Bend, Indiana.

Sophomore Class

Congratulations to Marvin Herz on his marriage to the former Miss Leslie Mittelman of The Bronx, New York, on September 13, 1952.

Congratulations to George Veldstra on his marriage to the former Miss Henrietta Enserink of Ripon, California, on June 18, 1952.

Best wishes to Mr. and Mrs. Burton Zeiger on their marriage on June 17, 1952. Mrs. Zeiger is the former Miss Lenore Kopstein of Chicago, Illinois.

Congratulations to Lawrence Zingesser on his marriage to the former Miss Virginia Bardes of Oakmont, Pennsylvania, on June 21, 1952.

The Quarterly

ORGANIZATION NEWS

Student Council Report

The Student Council has continued to function actively throughout the summer although handicapped by the absence of half of its membership. The main order of business has been consideration of the changes in the Student Council constitution which will be presented to the student body for ratification after the approval of the Administration has been obtained. These changes are designed to make the Student Council a more efficient organization so as to better serve the needs of the student body.

The various committees have also been active. The Internship Committee is busy studying the replies to the questionnaire sent by Dean Mullin, in which former graduates were asked to state their estimates of the merits of their internships.

The Orientation Committee has completed a draft of a program which the Student Council hopes can be integrated into the orientation program planned by the Administration for the incoming Freshman Class.

The Student Council Maurice Oppenheim Loan Fund has received a substantial contribution from Mr. Paul Bluth and the Class of 1952. This has more than doubled the usefulness of the Fund.

The Housing Committee has been working in close cooperation with Dean Ryan in an attempt to provide housing for the incoming freshmen. The Program Committee has been busy planning for the allotment of time and space to the various student organizations for their fall programs. Plans are also being made to publish another Student Directory this fall.

*Sheldon Waldman,
Temporary Secretary*

* * * * *

Phi Lambda Kappa

On May 24, 1952, Alpha Rho held its annual Senior Dinner Dance at the Furniture Club of America. Highlight of the evening was the presentation of the fraternity's First Annual Gold Medal Award to Dr. John J. Sheinin for his outstanding contributions to The Chicago Medical School.

Page Forty-seven

Our chapter has been active throughout the summer. On August 10th we had a beach party at Highland Park. The wives of our fraters have utilized this summer to carry out their plans to organize a Women's Auxiliary of the Alpha Rho Chapter. The girls sponsored a beach party-picnic on the week-end of August 23rd. Now that a Women's Auxiliary has been organized there have been some whisperings of organizing a Kiddies' Auxiliary as well, since the potential membership of such an organization is, at present, rising rapidly.

Plans have been made for the fall semester. A very complete and active program has been prepared and another successful year for PLK is anticipated. The fall program will get started on October 4th with a Smoker at the Congress Hotel.

We wish to extend our congratulations to the Freshman Class and offer Best Wishes for their future years at CMS.

Jerome Gold, Secretary

* * * * *

Phi Delta Epsilon

The formal activities of the Beta Tau chapter are rather dormant now. However, this is merely the "calm before the storm," for many plans are being made for a record-breaking string of activities to be inaugurated in the fall, among which are the smoker for incoming freshmen and prospective pledges and the fall pledge-dance. Many committees have been set up to administer these and other activities.

It is expected that the new pledge class will be even larger than the record-breaking class of last year, and with the already large chapter thus augmented further, the scope of its activities will be broadened correspondingly.

Beta Tau extends its sincerest congratulations to sophomore frater Burton Zenger on the occasion of his marriage to the former Lenore Kopstein of Chicago. Fraternally speaking, this is an extraordinary merger, since the groom was attended by two fraters, David Soll and Mel Goldzband, and the father of the bride, Dr. Ben Kopstein, is another Phi Dee E man.

Page Forty-eight

The chapter also wishes to congratulate Dr. John J. Sheinin, one of our more notable fraters, for the citation presented him by our cousins of Phi Lambda Kappa.

Melvin G. Goldzband, Historian

* * * * *

Association of Internes and Medical Students

The Chicago Medical School chapter of the Association of Internes and Medical Students is making plans for its Fall Quarter activities. The first job of the group will be to acquaint the incoming Freshman Class with the past and present work of the local and national organizations.

The activities of the chapter this year will gain added impetus from the presence in Chicago of the National President of AIMS, Louis Kolokoff—a CMS graduate who is serving a Medicine residency at Cook County Hospital.

Sanford Lazar, President

* * * * *

The Student American Medical Association

The Student American Medical Association continued its program of bringing stimulating motion pictures to the students during the summer. The films shown this summer were: *Shades of Gray*; *Poliomyelitis, Its Diagnosis and Treatment*; *Clinical Malaria*; *Endocrine Disorders*; and *Functional Anatomy of the Normal and Abnormal Heart*. The attendance at the Friday afternoon showings indicates that the students are interested in up-to-date medical motion pictures. Current plans call for the continuation of these programs during the school year.

With the beginning of the school year, there will be a membership drive to recruit new members and to renew old memberships. The S.A.M.A. Journal, which has enjoyed a huge success during its initial year, will begin its second volume with the October issue. Other benefits, including health insurance and scholarships, will be announced in the early issues of the S.A.M.A. Journal.

The officers for the summer were Jerome Gold, president, and Herbert Sohn and Helmut Stahlecker, vice-presidents.

Herbert Sohn, Vice-President

The Quarterly





THE CHICAGO MEDICAL SCHOOL QUARTERLY

710 South Wolcott Avenue
Chicago 12, Illinois

The Chicago Medical School *QUARTERLY* is published four times yearly by The Chicago Medical School for the dissemination of current medical news and for the advancement of medical science with a student staff under the supervision of a faculty editorial board.

STAFF

Arthur L. Pinchuck '53, Editor-in-Chief

Medical and Book Review Editor Robert J. Langs '53

Assistants Irwin Miller '53, Hubert B. Segal '54, Theodore
Feldman '54, Melvin H. Samuels '54, Edward Altchek '55

Features Editor Larry H. Shuman '54

Assistants Sheldon Waldman '55, Bernard Deitch '55

Business Managers Herbert A. Blough '55, David Lipton '55

EDITORIAL BOARD

Donald Atlas, M.D., Ph.D.

Piero P. Foa, M.D., Ph.D.

George Clark, Ph.D.

A. Robert Goldfarb, Ph.D.

Instructions to Contributors

Articles must be typewritten, double spaced, and the original copy submitted.

All articles are accepted on the condition that they are contributed solely to this publication.

A minimum number of illustrations will be furnished by the *QUARTERLY* provided the photographs or drawings are of suitable quality.

Reprints will be furnished by the *QUARTERLY* without charge and must be requested when the manuscript is submitted.

Manuscripts for publication should be addressed to The Editor, The Chicago Medical School *QUARTERLY*, 710 S. Wolcott Avenue, Chicago 12, Illinois.

January issue deadline is November 1, 1952.

April issue deadline is February 1, 1953.

Bibliographies must conform in style to that used in *Quarterly Cumulative Index Medicus*.

Permission must be obtained from the *QUARTERLY* for use of all or part of any articles in this publication. Permission will usually be granted provided proper credit is given.

LECTURE SERIES

The Chicago Medical School
710 South Wolcott Avenue

Wednesdays, 12:30 P. M.
Amphitheater A

HEART AND CIRCULATION II

- 1952
OCTOBER 1 Chemical Physiology of the Heart Muscle
Dr. Albert Szent-Gyorgyi,
Director, The Laboratory of the Institute for Muscle Research,
Woods Hole, Massachusetts
- OCTOBER 8 Experimental Hypertensions
Dr. George A. Wakerlin,
Professor and Chairman of the Department of Physiology,
The University of Illinois
- OCTOBER 15 The Physiological Basis for the Treatment of Peripheral Vascular Diseases
Dr. David I. Abramson,
Clinical Assistant Professor of Medicine, The University of Illinois; Attending Physician, Michael Reese and Hines Veterans' Hospitals; Associate Attending Physician, Mount Sinai Hospital
- OCTOBER 29 Etiology and Prophylaxis of Rheumatic Fever
Dr. Alvin F. Coburn,
Director, Rheumatic Fever Research Institute,
Municipal Contagious Hospital, Chicago, Illinois
- NOVEMBER 5 The Value of Angiography in the Diagnosis of Congenital Malformation of the Heart
Dr. Benjamin M. Gasul,
Director of Pediatric Cardiology,
Cook County Hospital, Chicago, Illinois
- NOVEMBER 12 The Therapy of Myocardial Infarction
Dr. William A. Brams,
Associate Professor of Medicine, Northwestern University;
Attending Physician, Michael Reese Hospital